	معاونت درمان تبریز Treatment Vice - Chancellor	**ایده های نوین پژوهشی** **در علوم پزشکی**

عنوان فارسی : **دستگاه تحریک مغناطیسی فراجمجمه ای مکرر rTMS**

عنوان انگلیسی : *Transcranial Magnetic Stimulation repetitive TMS*

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تحریک مغناطیسی مغز یا TMS به روشی غیر تهاجمی جهت تحریک مغز اطلاق می‌شود که بر اساس القای الکترومغناطیسی توسط یک سیم پیچ عایق صورت می‌گیرد. TMS مخففشده عبارت Transcranial Magnetic Stimulation به معنای تحریک مغناطیسی مغز فراجمجمه‌ای است.

این سیم پیچ Coil روی اسکالپ (پوست سر) و در نقطه‌ای منطبق بر ناحیه‌ای از مغز که در ایجاد علایم روانپزشکی یا عصبی دخیل هستند قرار می‌گیرد. کویل، پالس‌های مغناطیسی کوتاه مدتی ایجاد می‌کند که از لحاظ نوع و قدرت مشابه دستگاه تصویربرداری MRI است. هر پالس مغناطیسی به سهولت و بدون درد، از پوست سر و استخوان و پرده‌های مغز گذشته و به نورون‌های عصبی می‌رسد و باعث فعالیت کوتاه مدت نورون‌های عصبی مربوطه می‌گردد. چنانچه پالس‌ها بصورت متوالی و به سرعت تجویز شدند تحت عنوان تحریک مغناطیسی مغز مکرر repetitive TMS یا rTMS نامیده شده که قادر به ایجاد تغییرات پایدارتری در فعالیت مغزی است.

طبق مطالعات متعددی که در مورد اختلالات روانپزشکی و در زمینه متابولیسم مناطق مغزی مربوطه انجام شده، این نکته مطرح شده است که افزایش یا کاهش متابولیسم مناطق خاصی از مغز منجر به ایجاد علایم روانپزشکی می‌گردد.

به عنوان مثال افزایش فعالیت ناحیه پشتی جانبی پیش پیشانی راست یا کاهش فعالیت ناحیه پشتی جانبی پیش پیشانی چپ و یا عدم تقارن این دو ناحیه می‌تواند اختلال افسردگی اساسی ایجاد کند.

بر این اساس، با مهار یا تحریک مناطق مذکور می‌توان در تخفیف یا درمان اختلال مربوطه اقدام کرد. این عمل در تحریک مغناطیسی مغز rTMS با ایجاد میدان مغناطیسی و اعمال آن از روی پوست سر صورت می‌گیرد. فرکانس پالس ایجادشده (تعداد پالس در ثانیه) تعیین‌کننده خاصیت مهاری یا تحریکی بر روی نورون‌های مغزی است.

تحریک مغناطیسی مغز rTMS چه زمانی مورد استفاده قرار می گیرد؟

در بیماران افسرده‌ای که به یک دوره درمان دارویی یا روان درمانی پاسخ مناسبی نداده‌اند، rTMS می‌تواند به عنوان درمان کمکی یا جایگزین تجویز شود. تحریک مغناطیسی مغز rTMS توسط اداره غذا و داروی آمریکا FDA در اکتبر ۲۰۰۸ جهت درمان بیماران افسردگی اساسی که در اپیزود فعلی بیماری حداقل به یک دوره درمان کافی با داروی ضد افسردگی پاسخ نداده‌اند یا قادر به تحمل دارو نیستند، مورد پذیرش قرار گرفته است.

اثر بخشی تحریک مغناطیسی مغز rTMS در سایر اختلالات روانپزشکی مانندOCD ، اختلالات اضطرابی و توهمات شنوایی و علایم منفی بیماری اسکیزوفرنیا که به درمان دارویی مقاوم بوده‌اند، در مقالات مختلفی تأیید شده است

فرآیند درمان با تحریک مغناطیسی مغز rTMS چگونه است؟

تحریک مغناطیسی مغز rTMS در بیماران سرپایی و بستری قابل اجراست و بصورت جلسات درمانی متعدد تجویز می‌شود. در هر جلسه درمانی بیمار بر روی صندلی طراحی‌شده برای این امر (که بی‌شباهت با یونیت دندانپزشکی نیست) می‌نشیند. با توجه به ایجاد میدان مغناطیسی از بیمار خواسته می‌شود که قبل شروع فرآیند درمانی کلیه اشیاء حساس به مغناطیس (مانند کارت اعتباری و جواهرات ناحیه سر و گردن) را از خود دور کند. در صورت

امکان به وی محافظ شنوایی (پدهای داخل گوش) داده می‌شود تا از صدای پالس ایجادشده یا امواج مغناطیسی دچار آسیب احتمالی نگردد.

اپراتور سر بیمار را در وضعیت مناسبی قرار می‌دهد و اقدام به اندازه‌گیری پارامترهای خاصی بر روی جمجمه بیمار می‌نماید تا محل دقیق قرارگیری کویل دستگاه بر روی منطقه مورد نظر مغز مشخص شود. سپس شروع به تعیین آستانه حرکتی Motor Threshold بیمار نموده که عبارت است از حداقل قدرت مغناطیسی مورد نیاز جهت ایجاد انقباض در دست بیمار که از فردی به فرد دیگر فرق می‌کند. این عمل با تنظیم دستگاه جهت تولید تک پالس Single Pulse صورت می‌گیرد. تعیین آستانه حرکتی روانپزشک را قادر می‌سازد تا برنامه درمانی مختص هر فرد را طرح‌ریزی نماید تا بیمار میزان مناسبی از انرژی مغناطیسی را دریافت کند نه بیشتر از حد نیاز و نه کمتر از ایجاد اثرات درمانی.

پس از این اقدامات مجدداً کویل بر اساس اختلال روانپزشکی بیمار در محل مربوطه روی سر وی قرار می‌گیرد. در طی پروسه درمان، بیمار تنها صدای کلیک و ضربه مختصر ناشی از ایجاد پالس در ناحیه زیر کویل را احساس خواهد کرد.

در کل جلسه درمانی تحریک مغناطیسی مغزrTMS ، اپراتور حضور داشته و بیمار را پایش می‌کند و در صورت تمایل بیمار جلسه درمان را قطع می‌نماید. هر جلسه درمان ۴۰-۲۰ دقیقه طول می‌کشد و عموماً به میزان ۳-۵ روز در هفته تکرار می‌شود. کل دوره درمانی ۴-۶ هفته به طول می‌انجامد که بسته به نوع اختلال روانپزشکی، شدت آن و میزان پاسخ درمانی بیمار متغیر است.

مقدمه

تحریک مغناطیسی مغزی[1] یا «تی ام اس» یک روش غیرتهاجمی و درمانی بدون درد در بزرگسالان است. در این روش با استفاده از یک سیم‌پیچ عایق‌بندی‌شده که روی سر گذاشته می‌شود، در فواصل زمانی کوتاه میدان مغناطیسی ایجاد می‌گردد. استفاده از تحریک مغناطیسی مغزی فراجمجمه‌ای مکرر[2] یا آر تی ام اس در سال ۲۰۰۸ برای درمان افسردگی مقاوم به درمان در بزرگسالان و تحریک مغناطیسی مغزی فراجمجمه‌ای عمیق[3] یا دی تی ام اس درسال ۲۰۱۸ برای درمان اختلال وسواسی-اجباری مورد تأیید سازمان غذا و داروی ایالات متحده (FDA) قرار گرفت.

تحریک مغناطیسی مغزی یک روش درمانی غیرتهاجمی و بدون درد است که در آن مناطقی از مغز مورد هدف پالس‌های مغناطیسی قرار می‌گیرد. به دنبال این تحریک مغناطیسی جریان الکتریکی ضعیفی در مغز ایجاد می‌شود که مدارهای عصبی را به‌صورت کوتاه‌مدت فعال و یا مهار می‌کند.

الف) عنوان و کد ملی خدمت

تحریک مغناطیسی مغزی فراجمجمه‌ای مکرر (آرتی ام اس)

Transcranial Magnetic Stimulation repetitive

کد ملی: (۹۰۰۱۱۵)

ب) تعریف و تشریح خدمت مورد بررسی

در این روش درمانی با استفاده از یک سیم‌پیچ عایق‌بندی‌شده که در مجاورت سرگذاشته می‌شود، میدان مغناطیسی ایجاد می‌گردد. قدرت میدان مغناطیسی ایجاد شده توسط دستگاه تی ام اس مشابه اِم آر آی و تقریباً بی‌خطر است. بیمار بر روی یک صندلی قابل‌تنظیم می‌نشیند تا تحت درمان از طریق سیم‌پیچ دستگاه قرار گیرد.

میدان ضعیف مغناطیسی ایجاد شده توسط دستگاه تی ام اس به صورت متناوب تغییرجهت می‌دهد وتحریک مکرر در یک واحد زمانی کوتاه توسط دستگاه‌های تحریک مغناطیسی مغزی فراجمجمه‌ای مکرر (آرتی ام اس) انجام می‌شود. در این روش با فرکانس‌های بالا (بالاتراز ۵ هرتز) نورون‌ها تحریک می‌شوند و فرکانس‌های پایین (کمتر از یک هرتز) فعالیت نورون‌ها را کاهش می‌دهند.

درصورت استفاده از آر تی ام اس کاربرد هم‌زمان سایر درمان‌های دارویی و روان‌درمانی در روان‌پزشکی منعی ندارد، اما ضروری است به مصرف هم‌زمان داروهای پایین‌آورنده آستانه تشنج توجه شود.

ت) اقدامات یا پروسیجرهای ضروری جهت درمان بیماری

۱- ارزیابی پیش از پروسیجر

۱-۱- شرح حال بالینی و تشخیص‌گذاری

(الف) در ارزیابی پیش از انجام مداخله، لازم است شرح حال کامل روان‌پزشکی در زمان تشکیل پرونده، علایم اولیه، سابقه بیماری‌های روان‌پزشکی و جسمی، سابقه دریافت خدمات و درمان‌های دارویی که مراجع در گذشته دریافت کرده، درمان‌های اخیر، موارد اندیکاسیون وکنتراندیکاسیون و موارد احتیاط به‌دست آید.

(ب) در بررسی جامع ضروری است علاوه بر وضعیت روان‌پزشکی به نکات زیر هم توجه شود:

1. Transcranial Magnetic Stimulation (TMS)
2. repetitive Transcranial Magnetic Stimulation (rTMS)
3. deep Transcranial Magnetic Stimulation (dTMS)

۱-ب- شرایط دیگری که خطر تشنج را می‌افزاید:

- تاریخچه فردی صرع (بیماران درمان‌نشده‌ی مبتلا به یک یا چند اپیزود در گذشته)
- بیماران درمان‌شده‌ی ضایعات عروقی، جراحی، تومورها، عفونت‌ها و یا بیماری‌های متابولیک مغز، حتی بدون تاریخچه صرع
- استفاده از داروهایی که بالقوه آستانه تحریک تشنج را به میزان قابل توجهی کاهش می‌دهند؛ این داروها در بخش ژ ذکر شده‌اند.
- بی‌خوابی
- وابستگی به الکل

۲-ب- سایر عوامل مرتبط با شرایط بیمار یا بیماری:

- الکترودهای ایمپلنت‌شده در مغز (در قشر یا قسمت‌های عمیق مغز)
- بارداری
- بیماری قلبی شدید یا اخیر

(پ) به منظور بررسی هماهنگ ارزیابی پیش از انجام مداخله، می‌توان از پرسش‌نامه‌ی استاندارد غربالگری استفاده کرد (ضمیمه).

۱-۲- اخذ رضایت آگاهانه

در زمینه‌ی به‌کارگیری آرتی ام اس در بالین و پژوهش‌های انسانی لازم است دو مورد زیر رعایت شود:

(الف) کسب رضایت کتبی آگاهانه. تصمیم‌گیری افراد (یا نماینده قانونی آنها در مورد کودکان و افراد کم‌توان ذهنی) برای شرکت باید به‌صورت اختیاری و بر مبنای تأمین تمامی اطلاعات مربوطه و خطرات بالقوه باشد. در جریان رضایت آگاهانه، افراد باید اطلاعات را به شیوه‌ای دریافت نمایند که بتوانند روند کار، خطرات و مشکلات درمان را درک کنند. در متن رضایت‌نامه، باید در مورد خطرات، آسیب‌ها و همچنین مزایا و منافع درمان و هزینه آن در مقایسه با دیگر روش‌هایی که هنوز برای بیمار کاربرد دارد توضیح داده شود. برگه رضایت نامه باید در اختیار بیمار یا نماینده قانونی وی قرار داده شود و توسط آنها امضا شود.

(ب) سنجش نسبت سود به خطر. تنها کافی نیست که فرد مایل به پذیرش خطر موجود باشد. برای استفاده بالینی باید مزیت‌های بالینی بر خطرات بالقوه غالب باشد.

۱-۳- بررسی موارد اندیکاسیون و کنتراندیکاسیون (بخش‌های ج و ژ را ببینید.)

۱-٤- بررسی موارد احتیاط و ملاحظات مورد نیاز (بخش ژ را ببینید.)

۱-۵- تنظیم پروتکل درمانی

در تنظیم پروتکل درمانی، لازم است عوامل شدت، فرکانس، طول سلسله‌ها، مدت زمان بین سلسله‌ها و تعداد سلسله‌ها لحاظ شود. بر این اساس، پروتکل پیشنهادی درمان افسردگی به این شرح زیر است: «۳۰۰۰ پالس با فرکانس ۱۰ هرتز در قطارهای ٤ ثانیه‌ای با فاصله ۲٦ ثانیه و با شدت ۱۲۰ درصد آستانه حرکتی در هر جلسه با استفاده از کویل پروانه‌ای»
به منظور در نظر گرفتن ایمنی تحریک، لازم است پارامترهای جدول ۱ لحاظ شود.

۱-٦- بررسی عوامل خطر احتمالی و یا قطعی بروز تشنج

تذکر: پیش از انجام پروسیجر لازم است هر شش مورد فوق اجرا شده باشد. به بیان دیگر، لازم است این موارد به صورت چک‌لیست (سیاهه) ارایه شده و تیک زده شود و در جمع‌بندی نهایی، پزشک متخصص مسئول اجرای خدمت، جمع‌بندی کرده و مجاز بودن مداخله را امضا کند و در پرونده بیمار نگهدارد.

جدول ۱- حداکثر زمان ایمن (به ثانیه) در یک قطار منفرد تحریک rTMS: ایمنی به‌صورت نبود تشنج، عدم انتشار تحریک و دیس‌شارژ پس از تحریک در فعالیت الکترومیوگرافی تعریف می‌شود. اعداد نشانگر حداکثر تعداد پالس آزموده شده است.*

فرکانس (هرتز)	شدت (درصد آستانه حرکتی)				
	٪۹۰	٪۱۰۰	٪۱۱۰	٪۱۲۰	٪۱۳۰
۱	>۱۸۰۰	>۱۸۰۰	>۱۸۰۰	>۳۶۰	>۵۰
۵	>۱۰	>۱۰	>۱۰	>۱۰	>۱۰
۱۰	>۵	>۵	>۵	۴,۲	۲,۹
۲۰	۲,۰۵	۲,۰۵	۱,۶	۱,۰	۰,۵۵
۲۵	۱,۲۸	۱,۲۸	۰,۸۴	۰,۴	۰,۲۴

* روسی وهمکاران، ۲۰۰۹

۲- ارزیابی حین پروسیجر:

۱-۱- یافتن محل و آستانه تحریک

۲-۱- ارزیابی انجام صحیح تحریک

۳-۱- ارزیابی عوارض حین تحریک:

این ارزیابی شامل نظارت مستمر بر بیمار حین انجام آر تی ام اس ضروری است. وجود توییچ‌های عضلانی هم‌زمان با هر تحریک می تواند شاخص مهمی از انتشار فعالیت حرکتی برانگیخته باشد. هرچند تصویربرداری با ویدیو روش توصیه‌شده‌ای برای مراقبت است، مشاهده‌ی بیمار توسط یک شخص آموزش‌دیده حین انجام آر تی ام اس و گزارش موارد و نشانه‌های عوارض حین مداخله که می‌تواند پیش‌درآمد خطری برای فرد باشد به متخصص حاضر در درمانگاه یا در دسترس (آنکال)، کفایت می‌کند.

۳- ارزیابی پس از پروسیجر:

۱-۳- شناسایی و کنترل عوارض جانبی مداخله از طریق یک چک‌لیست مختصردر جلسات درمان: لازم است اثرات و عوارض جانبی مداخله به دقت بر اساس یک چک لیست ثبت شود. ارزیابی عوارض جانبی باید از جمله شامل سردرد، احساس درد در ناحیه پوست سر در محل تحریک، قرمزی ناحیه پوست سر در محل تحریک، گرفتگی عضلات صورت، احساس سبکی سر، تشنج، سنکوپ و حمله مانیا باشد.

۲-۳- هریک از درمانگاه‌های آر تی ام اس باید یک برنامه مشخص برای رسیدگی به سنکوپ یا تشنج داشته و همه اعضای تیم درمان باید با این عوارض آشنا باشند. ضروری است علاوه بر وجود تجهیزات استاندارد وزارت بهداشت برای این موارد، محلی برای دراز کشیدن بیماران وجود داشته باشد. تمامی اعضای تیم باید با وسایل کمک‌های اولیه پزشکی ومراقبت‌های اورژانسی اولیه آشنا باشند.

۳-۳- نتیجه‌ی ارزیابی لازم است به رؤیت پزشک معالج رسیده و پزشک معالج فرم را امضا نماید.

٤-۳- بررسی پیامدهای درمان با استفاده از ابزارها و پرسش‌نامه‌های معتبر، مانند نسخه فارسی آزمون‌های افسردگی بک و همیلتون، انجام می‌شود.

۵-۳- پذیرش نتیجه ارزیابی خطرات، اثرات و عوارض جانبی پس از مداخله، بر عهده‌ی پزشک درمان‌گر است. مصاحبه‌های ساختاریافته بیشتر ارزش پژوهشی دارد و برای پرهیز از صرف هزینه و زمان، اجرای آنها در درمان بالینی الزامی نیست.

پ) عوارض جانبی:

لازم به ذکر است اطلاعات موجود در مورد تحریک انفجاری تتا (TBS) هنوز برای اثبات بی خطر بودن این روش درمانی کافی نیست.

۱- شنوایی: از جمله فعالیت‌های بالقوه خطرناک مرتبط با تی ام اس، تولید امواج صوتی با دامنه زیاد و شدید است که ممکن است از میزان ۱٤۰ دسی‌بل تجاوز کند. این میزان فراتر از سطوح توصیه‌شده‌ی ایمنی برای سیستم شنوایی (OSHA) است. بعد از مواجهه با محرک های تی ام اس، درصد اندکی از افراد بزرگسال افزایش موقتی در آستانه شنوایی خود را ذکر کرده‌اند ولی تغییر دائمی آستانه در افرادی که پلاک‌های محافظ شنوایی نداشته و تحریک در آنها با سیم‌پیچ اچ‌شکل انجام گرفته، دیده شده است. در بیشتر پژوهش‌هایی که در آنها محافظ شنوایی به‌کار گرفته شده بود، تغییری در شنوایی را پس از تی ام اس گزارش نکردند. بنابراین توصیه می‌شود که:

۱-۱- ملاحظات مربوط به ایمنی شنوایی باید از طریق موارد زیر مورد نظر قرار گیرند:

(الف) استفاده از محافظ تأیید شده (پلاگ‌های گوشی یا پوشش گوش) توسط افراد آموزش‌دیده برای جاگذاری این ابزارها

(ب) مراجعه سریع به منظور ارزیابی شنوایی برای تمام افرادی که از کم‌شنوایی، وزوز گوش یا صدای دائمی پس از انجام تی ام اس شکایت دارند.

(پ) افرادی که از قبل در اثر کم‌شنوایی صدایی در گوش خود می‌شنیدند یا هم‌زمان داروهایی دریافت می‌کردند که اثر سمی بر گوش داشتند، همانند آمینوگلیکوزیدها وسیس‌پلاتین، باید تنها در صورتی تی ام اس دریافت کنند که نسبت فایده به خطر مطلوب باشد؛ همانند زمانی که آر تی ام اس در درمان وزوز گوش استفاده می‌شود.

۲-۱- افرادی که ایمپلنت‌های مجرای حلزونی دارند نباید از آر تی ام اس استفاده کنند.

۳-۱- ملاحظات مربوط به ایمنی شنوایی کودکان به کفایت در مقالات فعلی مطرح نشده است؛ لذا ضروری است اطلاعات بیشتری در زمینه ایمنی در کودکان فراهم شود. استفاده از آر تی ام اس در بیماران خردسال به منظور درمان ممکن است در صورتی منطقی باشد که مزایای بالقوه بر خطرات ناشی از مشکلات شنوایی ارجح باشند.

۲- تشنج: القای تشنج مهم‌ترین عارضه تی ام اس است. موارد متعددی از تشنج‌های تصادفی القاشده به‌وسیله تی ام اس تا به امروز گزارش شده است. با در نظر گرفتن تعداد زیاد افراد و بیمارانی که از سال ۱۹۸۸ با کارآزمایی‌های تی ام اس مورد بررسی قرار گرفته‌اند و تعداد کم موارد تشنج، می‌توان برآورد کرد خطر تی ام اس برای القای صرع بی‌تردید خیلی پایین است. به‌نظر می‌رسد زمانی که پالس‌ها با فرکانس‌های نسبتاً بالا و دوره‌های کوتاه بینابینی بین سلسله تحریک‌ها انجام می‌شوند ممکن است تی ام اس موجب بروز تشنج شود. به‌طورخلاصه می‌توان اشاره کرد ایجاد تغییرات الکتروآنسفالوگرافی به صورت تشنج کلاسیک در طول درمان تی ام اس بسیار نادر است و استفاده از الکتروآنسفالوگرافی قبل و در طول تی ام اس نمی‌تواند برای جلوگیری از القای تشنج احتمالی روشی کارآمد باشد.

۳- سنکوپ: سنکوپ (نوروکاردیوژنیک) یک واکنش عادی نسبت به اضطراب و اتفاقات ناخوشایند است. سنکوپ تجربه‌ای رایج است که می‌تواند بیش از تشنج‌های صرعی، در طول آزمایش و درمان تی ام اس همانند سایر مداخلات پزشکی رخ دهد. دراین موارد فرد ممکن است رفتارهایی همانند تشنج مثل سفت شدن تونیک، انقباض، اتوماتیسم گفتاری و حرکتی، تاری دید و سردرد، بی‌اختیاری، توهم و آسیب‌های ناشی از سقوط از خود نشان دهد. تمایز چنین حملاتی از حملات تشنج می‌تواند دشوار باشد. به لحاظ بالینی، ویژگی اصلی متمایزکننده‌ی سنکوپ، برگشت سریع هوشیاری ظرف چند ثانیه و کمتر از یک دقیقه است. درصورت بروز سنکوپ، تی ام اس باید بلافاصله خاتمه یابد. راه‌های هوایی و گردش خون باید ارزیابی شوند. فرد جز در مواقعی که دچار تشنج تونیک کلونیک است به یک طرف برگردد تا به پاک‌سازی راه‌های هوایی و جلوگیری از آسپیراسیون کمک شود. افرادی که دچار تشنج هستند باید به محض این که حرکات متوقف شد، به یک‌طرف برگردند و در آن موقعیت باقی بمانند تا هوشیاری‌شان بازگردد. برگشت تأخیری هوشیاری در بیش از ۳۰ ثانیه پس از تشنج، به ارزیابی‌های بالینی بیشتری نیاز دارد.

٤- درد موضعی و سردرد: سردرد مربوط به تی ام اس تک‌پالس معمولاً به‌خوبی تحمل می‌شود و بیشتر افراد بدون درد هستند. برخی از مشکلات ممکن است در زمان استفاده از تکنیک تحریک سه‌گانه (stimulation technique triple)، به دلیل آستانه بالاتر محرک‌های محیطی ایجاد شوند.

برخی اوقات تی ام اس و به‌ویژه آر تی ام اس می‌تواند دردناک باشد. این مسأله در حقیقت رایج‌ترین عارضه جانبی تی ام اس است. شدت دردی که تجربه می‌شود، بسته به حساسیت هر فرد، موقعیت سر، طراحی سیم‌پیچ و شدت و فرکانس تحریک در هر فرد متفاوت است. بیماران باید به این موضوع آگاه باشند که تی ام اس می‌تواند موجب درد شود.

تحریک حسی پوست زمانی ایجاد می‌شود که آر تی ام اس عضلات جمجمه را تحریک می‌کند و انقباضی را در اسکالپ یا قسمت بالایی صورت ایجاد می‌نماید که می‌تواند برای برخی افراد دردناک باشد و برای برخی دیگر نباشد. اما این عارضه با توجه به بی‌خطر بودن، قابل چشم‌پوشی است. در کارآزمایی‌های بالینی تی ام اس تا به امروز، تنها درصد کمی از بیماران به دلیل درد درمان را در طول دوره تی ام اس قطع کرده‌اند. در تعداد زیادی از بیماران، درد موضعی در خلال مداخله تی ام اس، از جمله دندان‌درد ایجاد می‌شود، ولی این اثرات به سرعت از بین می‌رود. سردرد گاهی ممکن است پس از اتمام جلسه نیز ادامه داشته باشد. در این موارد مصرف یک مسکن رایج به شکل خوراکی می‌تواند مفید باشد. شواهد حمله میگرنی پس از آر تی ام اس در افراد طبیعی و در بیماران مبتلا به میگرن گزارش نشده است. درد موضعی قسمت پیشانی همراه با درمان تی ام اس در طول اولین روزهای درمان تخفیف می‌یابد. به همین دلیل در برخی الگوریتم‌های درمانی با تحریکات افزایش‌یابنده، تحریک را زیر دوز هدف شروع می‌کنند و به‌تدریج در طول اولین هفته درمان افزایش می‌دهند.

۵- تغییرات شناختی: مجموعه‌ای بزرگ از داده‌های تجربی برای استفاده از تی ام اس فراتر از تک‌پالس، پالس مضاعف، و آر تی ام اس یک هرتزی در علوم روان‌شناسی و شناختی گردآوری شده است و مشاهده شده که تنظیم پارامترها در کاهش عوارض اهمیت دارد. مدت زمان کوتاه سلسله‌ها و فواصل طولانی درون‌سلسله‌ای موجب کاهش خطر می‌شود. در درمان تی ام اس و آر تی ام اس عوارض جانبی به‌گونه‌ای غیرقطعی با علایم شناختی همانند خستگی فزاینده ذهنی، مشکلات تمرکز و مشکلات حافظه ارتباط داشتند، هرچند این موارد، خفیف، موقتی و «بسیار نادر» بودند.

۶- تغییرات حاد روان‌پزشکی: در مواردی بروز مانیا در فرکانس‌های بالا و پایین آر تی ام اس در بیماران مبتلا به افسردگی تک قطبی و دوقطبی پس از تحریک قشر چپ پیشانی دیده شده است. اگرچه یک مطالعه ارتباط علت و معلولی میان آر تی ام اس و مانیا را مطرح می‌کند، به‌نظر می‌رسد میزان کلی (۱۳ مورد از میان ۵۳ مورد پژوهش کنترل‌شده و تصادفی‌شده در افسردگی) پایین باشد و این مقدار حتی پایین‌تر از میزان طبیعی سوییچ در بیماران مبتلا به اختلالات دوقطبی تحت درمان با داروهای تثبیت‌کننده‌ی خلق است. به‌همین ترتیب، مواردی از اضطراب، بی‌قراری، افکار خودکشی و بی‌خوابی به دنبال درمان با آر تی ام اس گزارش شده است، اما مشخص نیست که این موارد در مقایسه با سیر طبیعی بیماری هنگام درمان و یا عوارض سایر مداخله‌ها بیشتر باشد. علائم سایکوتیک و افکار خودکشی در افراد طبیعی در طول آر تی ام اس یا بعد از آن گزارش نشده است.

ث) تواتر ارائه خدمت (تعداد دفعات مورد نیاز / فواصل انجام):

انجام مداخله آرتی ام اس نیاز به اقامت و بستری ندارد و به‌صورت سرپایی انجام می‌شود. برای اختلال افسردگی عمده مقاوم به درمان، یک دوره درمانی شامل پانزده جلسه به صورت پنج جلسه در هفته، در طی سه هفته متوالی توصیه می‌شود.

ج) موارد انجام مداخله درمانی (اندیکاسیون‌ها):

۱- **اختلال افسردگی مقاوم به درمان در افراد ۱۸ ساله یا بزرگ‌تر:** در این استاندارد براساس شواهد موجود، منظور از اختلال افسردگی مقاوم به درمان، مواردی از اختلال افسردگی عمده (Major Depressive Disorder) است که دست‌کم به یک دوره‌ی درمان دارویی ضدافسردگی استاندارد، با دوز کافی درمانی و زمان کافی (حداقل ٤ تا ٦ هفته) پاسخ نداده است. لازم است تأکید شود این اندیکاسیون شامل اختلالات افسردگی زیر نمی‌شود:

(۱) نوع دوقطبی؛ (۲) همراه با علایم سایکوتیک؛ (۳) موارد نیازمند مداخله فوری؛ (٤) ثانوی به سوءمصرف مواد

۲- **دی تی ام اس برای اختلال وسواسی-اجباری در افراد ۱۸ ساله یا بزرگ‌تر:** ماشین‌های این نوع از تی ام اس‌ها با آر تی ام اس متفاوت‌اند و نیاز به استفاده از ماشین‌های تأییدشده‌ی وزارت بهداشت، درمان و آموزش پزشکی برای این منظور دارند.

چ) افراد صاحب صلاحیت جهت تجویز (Order) خدمت:

متخصصان روان‌پزشکی

ح) افراد صاحب صلاحیت اصلی جهت ارائه خدمت:

متخصصان روان‌پزشکی

جدول ۲– عنوان و سطح تخصص‌های مورد نیاز (استاندارد) برای اعضای غیرروان‌پزشک تیم ارائه‌کننده خدمت

ردیف	عنوان تخصص	تعداد به ازای ارائه خدمت	تحصیلات مورد نیاز	گواهی ضروری	آگاهی و سابقه کار	نقش در فرایند ارائه خدمت
۱	پزشک عمومی*	۱	دکترای حرفه‌ای پزشکی عمومی	گواهی گذراندن دوره‌ی تی‌ام‌اس	آشنایی با مبانی فیزیولوژی مغز، مدیریت تشنج و سنکوپ و کار با دستگاه آرتی‌ام‌اس	انجام مداخله
۲	کارشناس*	۱	کارشناسی رشته‌های پزشکی، پیراپزشکی یا روان‌شناسی	گواهی گذراندن دوره‌های کمک‌های اولیه و تی‌ام‌اس	آشنایی با مبانی فیزیولوژی مغز، مدیریت تشنج و سنکوپ و کار با دستگاه آرتی‌ام‌اس	انجام مداخله

* پزشک عمومی یا کارشناس به‌تنهایی و بدون حضور روان‌پزشک نمی‌تواند اقدام به تحریک مغناطیسی مغز نماید.

– پزشکان عمومی و کارشناسان رشته‌های پزشکی، پیراپزشکی و روان‌شناسی در صورت احراز شرایطی دارای صلاحیت ارائه خدمت می‌شوند. این گروه ضروری است آموزش‌های مدونی حداقل به مدت سی ساعت شامل مباحث نظری و عملی درمان با آر تی ام اس را بگذرانند. این دوره‌های آموزشی می‌تواند توسط انجمن علمی روان‌پزشکان ایران، انجمن پزشکی روان‌تنی ایران و گروه‌های آموزشی روان‌پزشکی دانشگاه‌های علوم پزشکی دارای استاندارد آموزش تی ام اس ارایه شود. در این دوره‌ها، کارکنان درمانگاه باید برای شناخت و مدیریت صرع یا سنکوپ آموزش ببینند و با آخرین پروتکل‌ها و راهنماهای بالینی درمان افسردگی مقاوم به درمان و هر اندیکاسیون دیگری آشنا شوند.

– توصیه می‌شود که تمامی کاربران تی ام اس، دانش ابتدایی فیزیولوژی مغز، مکانیسم‌های ابتدایی تی ام اس و پتانسیل خطر فرایند و تغییرات فیزیولوژیکی القاشده را بدانند (جدول ۲).

– کاربران غیرپزشک تی ام اس، باید دوره‌ی کمک‌های اولیه را گذرانده باشند.

– تمامی کارکنان درمانگاه باید دسترسی کامل به وسایل حمایت از زندگی و تجهیزات احیای اورژانسی داشته باشند.

خ) استانداردهای فضای فیزیکی و مکان ارائه خدمت

۱– به مجموعه پزشکی (بیمارستان یا درمانگاه مجهز برای بیماران سرپایی) برای تمامی موارد استفاده از آر تی ام اس (تشخیصی یا مداخله‌ای) نیاز است. درمان‌های آر تی ام اس بیماران سرپایی را می‌توان در خارج از بیمارستان انجام داد. اما اکیداً توصیه می‌شود که در این مجموعه‌ها و دیگر محیط‌های پزشکی، تجهیزات احیای قلبی–تنفسی و ترالی اورژانس پزشکی وجود داشته باشد.

۲– برای انجام این روش به یک فضای فیزیکی مجزا با مساحت کافی (حداقل سه متر در چهار متر) جهت استقرار دستگاه تی ام اس، ترالی اورژانس و وسایل کامل احیا، تخت معاینه، فرد مراجعه‌کننده و فرد ارایه‌دهنده‌ی خدمت نیاز است. لازم به ذکر است در صورتی که

مداخله در بیمارستان یا درمانگاه «مجهز به اتاق احیای مجزا و در نزدیکی محل انجام تی ام اس» صورت می‌گیرد، در صورتی که انتقال بیمار به محل مورد نظر در حداقل زمان ممکن قابل انجام باشد، وجود ترالی اورژانس در اتاق مداخله ضروری نیست.

۳- فضای فیزیکی مناسبی حداقل به مساحت ۱۲ مترمربع به عنوان اتاق انتظار بیماران مورد نیاز است.

د) تجهیزات پزشکی سرمایه‌ای به ازای هر خدمت

۱- دستگاه تحریک مغناطیسی مغز: مورد تأیید وزارت بهداشت، درمان و آموزش پزشکی

۲- کویل مخصوص

۳- صندلی قابل تنظیم

٤- ترالی اورژانس و تجهیزات و وسایل کامل احیای قلبی-تنفسی

ذ) داروها، مواد و لوازم مصرفی پزشکی جهت ارائه هر خدمت (جدول ۳)

جدول ۳- داروها، مواد و لوازم مصرفی پزشکی جهت ارائه خدمت آر تی ام اس

ردیف	اقلام مصرفی مورد نیاز	میزان مصرف (تعداد یا نسبت)
۱	تجهیزات احیا و داروها (فهرست مربوط به ترالی اورژانس از وب سایت معاونت درمان وزارت بهداشت تهیه شود و در ضمایم قرار گیرد.)	در صورت تشنج یا سنکوپ
۲	گوش‌گیر (ear pl ug)	یک عدد برای هر بیمار جهت استفاده حین انجام تحریک مغناطیسی مغز
۳	کلاه شنا	یک عدد برای هر بیمار جهت استفاده حین انجام تحریک مغناطیسی مغز

ر) اقدامات پاراکلینیکی، تصویربرداری و دارویی مورد نیاز پیش از ارائه خدمت

نیاز به اقدام پاراکلینیکی و تصویربرداری خاصی پیش از ارایه خدمت نیست. تنها لازم است داروهای مصرفی بیمار بررسی شود و در صورت مصرف داروهای کاهش‌دهنده‌ی آستانه تشنج، تجویز آنها مدیریت شود.

ز) استانداردهای گزارش (شامل مشاهده‌ها و اندازه‌گیری‌های ضروری)

در گزارش مداخله لازم است شرح حال کامل روان‌پزشکی در زمان تشکیل پرونده، علایم اولیه، سابقه بیماری‌های روان‌پزشکی و جسمی، سابقه دریافت خدمات و درمان‌های دارویی که مراجع در گذشته دریافت کرده، درمان‌های اخیر، رضایت آگاهانه، پروتکل درمانی، ارزیابی پیش، حین و پس از مداخله، نتایج کوتاه‌مدت و بلندمدت درمانی و برنامه درمان دارویی در آینده قید شود.

ژ) ممنوعیت‌های (کنتراایندیکاسیون‌های) تجویز خدمت:

۱- افکار خودکشی و خطر اقدام به خودکشی

۲- مصرف داروهای پایین‌آورنده‌ی آستانه تشنج: در ادامه، فهرستی از داروها که بر پایه دانش کنونی در صورت استفاده هم‌زمان با آر تی ام اس می‌تواند خطرآفرین باشد آورده شده است. بی‌تردید این فهرست با پیشرفت مطالعات، تغییر خواهد کرد.

۲-۱- مصرف یکی از این داروها یا ترکیب آنها به دلیل احتمال کاهش قابل‌توجه آستانه تشنج، دارای پتانسیل خطر قوی است: ایمی‌پرامین، آمی‌تریپتیلین، دوکسپین، نورتریپتیلین، کلرپرومازین، کلوزاپین، فوسکارنت، گانسیکلوویر، ریتوناویر، آمفتامین‌ها، کوکائین، اکستازی (MDMA)، فن سیکلیدین (PCP، گرد فرشته)، کتامین، گاماهیدروکسی بوتیرات (GHB)، الکل و تئوفیلین. در چنین مواردی، در صورت نیاز، آر تی ام اس با احتیاط‌های ویژه‌ای باید انجام شود.

۲-۲- مصرف یک یا ترکیبی از داروهای زیر به دلیل کاهش نسبی پتانسیل آستانه تشنج، دارای پتانسیل خطر نسبی است: میانسرین، فلوکستین، فلووکسامین، پاروکستین، سرترالین، سیتالوپرام، ربوکستین، ونلافاکسین، دولوکستین، بوپروپیون، میرتازاپین، فلوفنازین، پیموزاید، هالوپریدول، اولانزاپین، کوتیاپین، آریپیپرازول، زیپراسیدون، ریسپریدون، کلروکین، مفلوکین، ایمی‌پنم، پنی‌سیلین، آمپی‌سیلین، سفالوسپورین، مترونیدازول، ایزونیازید، لووفلوکساسین، سیکلوسپورین، کلرامبوسیل، وین کریستین، متوترکسات، سیتوزین آرابینوزید، لیتیوم، آنتی‌کولینرژیک‌ها، آنتی هیستامین‌ها و مقلدهای سمپاتیک. در چنین مواردی در صورت نیاز، آر تی ام اس باید با احتیاط استفاده شود.

۲-۳- قطع هریک از مواد/داروهای زیر به دلیل کاهش قابل‌توجه آستانه تشنج، منجر به خطر نسبتاً زیاد می‌شود: الکل، باربیتورات‌ها، بنزودیازپین‌ها، میروبامات و کلرال هیدرات. در موارد حذف داروهای مذکور به لحاظ بالینی یا علمی، باید آر تی ام اس در صورت نیاز با احتیاط استفاده شود.

۳- سابقه تشنج در فرد یا خانواده

٤- وجود علایم حاد سایکوتیک یا مانیا

۵- بارداری: میدان‌های مغناطیسی با توجه به فاصله‌ای که از جنین وجود دارد تضعیف می‌شود، بنابراین تأثیر مستقیم تی ام اس بر جنین نامحتمل به نظر می‌رسد. گزارش‌هایی از زنان بارداری که درمان موفقیت‌آمیز افسردگی با آر تی ام اس را بدون هیچگونه عارضه جانبی برای کودکشان پشت سر گذاشتند وجود دارد. با این‌حال، بهتر است دیدگاهی محافظه‌کارانه را در مورد استفاده از آر تی ام اس در بارداری، با توجه به نسبت فایده به خطر آن در نظر گرفت. زنان بارداری که به عنوان اوپراتورهای تی ام اس کار می‌کنند باید به شکل محافظتی حداقل ۷۰ سانتیمتر دور از سیم‌پیچ تخلیه قرار بگیرند.

٦- کودکان: باتوجه نبود شواهد کافی در ایمن بودن به‌کارگیری آر تی ام اس در کودکان و احتمال آسیب شنوایی، این مداخله درمانی برای کودکان قابل انجام نیست.

۷- وجود اشیا فلزی در بدن در فاصله ۳۰ سانتی‌متری محل قرارگیری کویل شامل:

۷-۱- کلیپس آنوریسم

۷-۲- استنت‌های گردن یا مغز

۷-۳- ضربان‌ساز قلبی یا دفیبریلاتورهای قلبی

۷-٤- ایمپلنت حلزون گوش

۷-۵- وجود ترکش

تذکر: تنها تداخل مطلق با تی ام اس یا آر تی ام اس، وجود سخت‌افزار فلزی است که تماس نزدیکی با سیم‌پیچ تخلیه‌ای دارد (مثل ایمپلنت‌های حلزونی، ژنراتور پالس داخلی یا پمپ‌های پزشکی). در چنین مواردی خطر القای سوءعملکرد چنین ابزارهای ایمپلنت شده‌ای وجود دارد.

۸- خالکوبی صورت با استفاده از جوهر حساس به میدان مغناطیسی

س) مدت زمان ارائه هر واحد خدمت

مدت زمان ارایه خدمت براساس نوع پروتکل بین ۱۵ تا ٤۰ دقیقه در هرجلسه درمانی است.

ش) آموزش بیمار

۱- لازم است آموزش بیمار در مورد روش درمانی تی ام اس، نحوه اثربخشی، عوارض جانبی و روش‌های جایگزین انجام شود.

۲- آگاه کردن بیمار از اندیکاسیون‌های استاندارد تی ام اس و ثبت این موضوع در پرونده او ضروری است.

۳- توصیه می‌شود پمفلت آموزشی در اختیار بیماران قرار گیرد.

٤- پیشنهاد می‌شود از فیلم آموزشی جهت آموزش بیماران استفاده شود.

ضمیمه

پرسش‌نامه استاندارد غربالگری کاندیداهای آرتی ام اس*:

درمانگر باید استفاده از یک پرسش‌نامه استاندارد برای غربالگری کاندیداهای آر تی ام اس را در نظر داشته باشد. سؤالات زیر معرف اطلاعات پایه مورد نیاز است. اطلاعات مازاد لازم ممکن است بر اساس نیازهای خاص تغییر کنند، اما منابع، اجماع بر موارد زیر را نشان می‌دهند.

۱- آیا شما صرع دارید یا تا به حال دچار تشنج شده‌اید؟

۲- آیا تا به حال حملات سنکوپ یا غش را تجربه کرده‌اید؟ اگر بله، لطفاً توضیح دهید در چه موقعیت‌هایی؟

۳- آیا تا به حال آسیب مغزی شدید (یعنی همراه با بیهوشی) داشته‌اید؟

٤- آیا مشکل شنوایی دارید یا در گوش خود صدای زنگ می‌شنوید؟

۵- آیا باردار هستید و یا احتمال آن وجود دارد؟

٦-آیا در مغز/جمجمه شما فلز (به‌جز تیتانیوم) کار گذاشته شده است؟ (مانند کلیپس‌ها، تکه‌ها، تراشه‌ها)

۷- آیا ایمپلنت مجرای حلزونی دارید؟

۸- آیا ایمپلنت محرک عصبی دارید؟ (مانند دستگاه دی بی اس [DBS] اپی‌دورال یا ساب‌دورال و دستگاه وی ان اس [VNS])

۹- آیا دستگاه ضربان‌ساز قلبی (pace maker) یا خطوط درون‌قلبی یا هر نوع فلزی در بدن‌تان دارید؟

۱۰- آیا شما ابزار تزریق داخل وریدی دارو دارید؟

۱۱- آیا دارویی مصرف می‌کنید؟ (لطفاً فهرست کنید.)

۱۲- آیا تا به حال عمل جراحی در کانال نخاعی خودتان داشته‌اید؟

۱۳-آیا دچار انحراف بطنی یا نخاعی هستید؟

۱٤- آیا پیش از این از تی ام اس استفاده کردید؟

۱۵- آیا تا به حال MRI انجام داده‌اید؟

* پاسخ‌های تأییدی به یک یا چند مورد از سؤالات ۱ تا ۱۳ به معنای منع مطلق تی ام اس نیست، اما نسبت سود وخطر باید به‌دقت به‌وسیله پزشک مسئول (درمان‌گر) و یا محقق اصلی پروژه پژوهشی سنجیده شود.

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- **تاریخ اعتبار این راهنما از زمان ابلاغ به مدت سه سال است و پس از آن باید به‌روزرسانی شود.**

rTMS تحریک مغناطیسی مغز است که در طی آن فعالیت الکتریکی مغز تحت تأثیر میدان مغناطیسی قرار می گیرد.

میدان مغناطیسی از طریق جریان پالس هایی از سر عبور می کند.

در طی این روش میدان مغناطیسی می‌تواند نواحی خاصی از قشر مغز را تحریک کند.

هر پالس مغناطیسی به راحتی و بدون احساس درد، از پوست سر و استخوان و پرده های مغز گذشته و به نورون های عصبی می رسد و موجب فعالیت کوتاه مدت نورون های عصبی آن قسمت از مغز می شود.

میدان مغناطیسی که در نتیجه rTMS ایجاد می‌شود علاوه بر ایمن بوده احساس ناخوشایندی نیز در فرد ایجاد نمی کند.

عبور میدان مغناطیسی از مغز سبب ایجاد جریانی در سلول های عصبی مغز می‌شود و این سلول ها را تحریک می کند.

rTMS می‌تواند برای هر بیمار بطور اختصاصی و در منطقه خاصی از مغز انجام بگیرد.

این روش درمانی بسته به نوع بیماری یا اختلال می تواند تاثیرات اختصاصی بازدارنده یا تحریکی بر آن قسمت از مغز بگذارد.

بر اساس تحقیقات انجام گرفته افزایش یا کاهش متابولیسم مناطق خاصی از مغز می تواند سبب بروز مشکلات روانپزشکی همچون افسردگی در افراد شود که با روش rTMS قابل درمان است.

rTMS در بیمارانی که نسبت به درمان دارویی افسردگی پاسخ مثبت نداده اند به عنوان یک روش موثر کاربرد دارد.

امروزه افسردگی یکی از شایع ترین بیماری های روانی در جهان محسوب می شود. که بر اساس آمارها ۳۵۰ میلیون نفر که ۵ درصد جمعیت کل جهان را تشکیل می دهند از آن رنج می برند.

درمان از طریق تحریک الکترو مغناطیسی مغز توسط دستگاه rTMS بهترین درمان افسردگی از سال ۲۰۰۸ شناخته شده است که مورد تایید سازمان غذا و دارو آمریکا نیز رسیده است.

تحریک الکترومغناطیسی مغز توسط دستگاه tms میتواند به عنوان یک عامل خارجی فعل و انفعالات نورون ها را به حالت طبیعی برگرداند و بیماری هایی همچون سکته مغزی، وزوزگوش ، افسردگی، وسواس ،اضطراب و اختلال دوقطبی را درمان کند.

rTMS

پارامترهای تحریک rTMS

تعداد و شدت تحریک ها

فرکانس تحریک ها

فواصل بین تحریک ها

مناطق مورد تحریک در مغز

موارد کاربرد rTMS

افسردگی

اختلال وسواس

اختلالات اضطرابی

توهمات شنوایی

اسکیزوفرنی مقاوم به درمان دارویی

آسیب های مغزی مانند سکته مغزی

پارکینسون

اختلال دوقطبی

درمان دیسفاژی پس از سکته مغزی

سردردهای میگرنی

صرع

اضطراب

توهم

فلج صورت

مزایای درمانی rTMS

تاثیرات درمانی چشمگیر در زمان کم

کم عارضه ، بدون درد و غیر تهاجمی

غیر سیستمیک است و چیزی وارد جریان خون نمی‌شود.

عدم نیاز به بیهوشی (قابل انجام بصورت سرپایی)

تاثیر درمانی قابل توجه در بیماران مقاوم به درمان های دارویی

عوارض جانبی داروها مانند افزایش وزن، خواب‌آلودگی، بی‌خوابی، ناراحتی معده یا مشکلات جنسی در این روش ایجاد نخواهد شد.

مکانیسم درمان با rTMS

برای انجام فرایند تحریک مغناطیسی مغز بیمار بر روی صندلی مخصوصی قرار گرفته و کویل دستگاه بر روی منطقه مورد نظر مغز قرار میگیرد.

قبل از شروع پروسه درمان نیز بیمار باید اشیا حساس به جریان مغناطیسی مانند جواهرات و یا کارت های اعتباری را از خود دور کند.

تعداد جلسات درمانی با این روش فرد به فرد متفاوت است و بسته به نوع اختلال و آسیب مدنظر و با تشخیص متخصص مغز و اعصاب تعیین می شود.

بسمه‌تعالی

فرم تدوین راهنمای تجویز

عنوان استاندارد	کد RVU	کاربرد خدمت		افراد صاحب صلاحیت جهت تجویز	ارائه‌کنندگان اصلی صاحب صلاحیت	شرط تجویز		محل ارائه خدمت	تواتر خدمتی		مدت زمان ارائه	توضیحات
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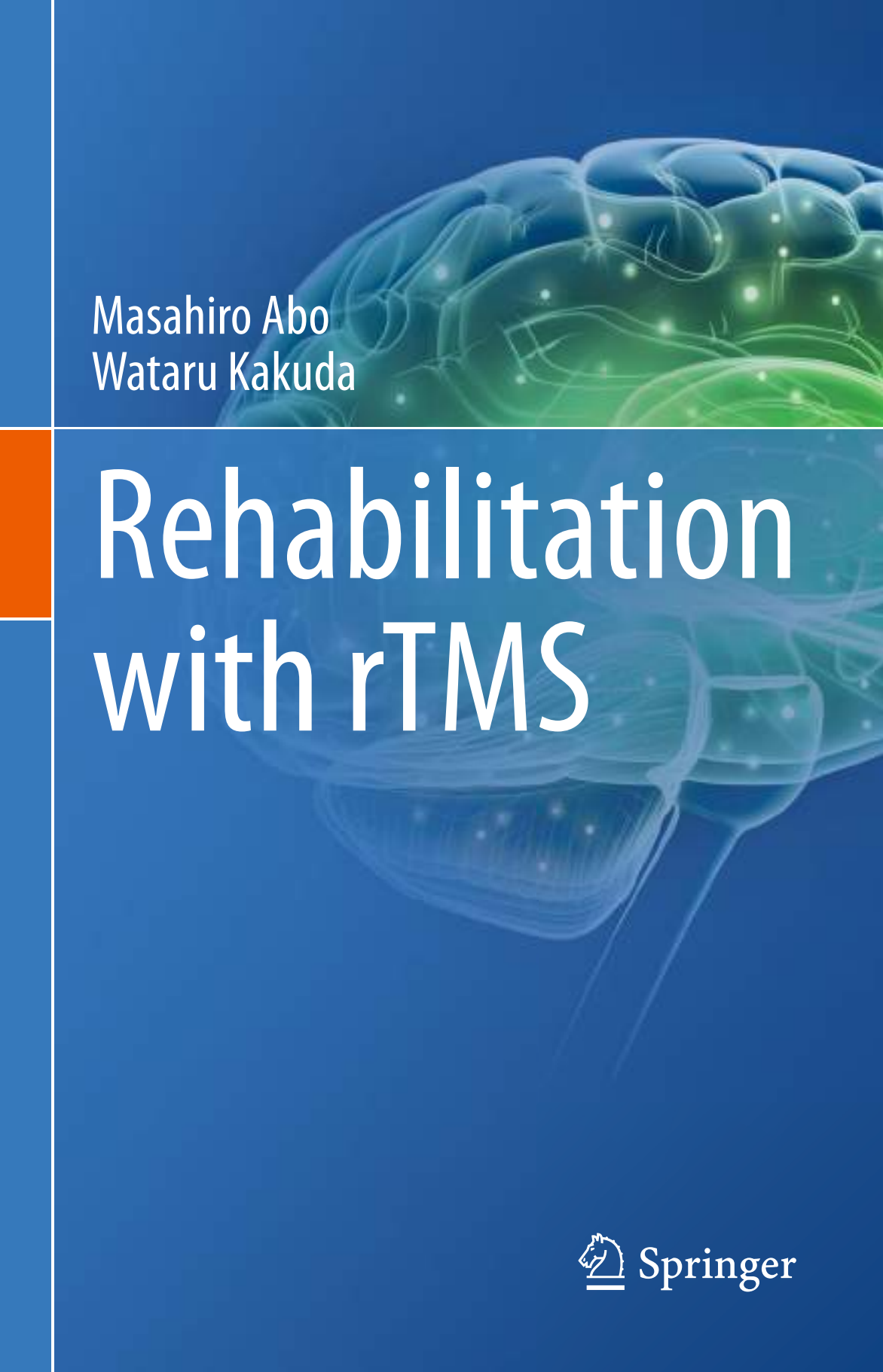
آرتی ام اس	۹۰۰۱۱۵	*	*	روان‌پزشک	روان‌پزشک	اختلال افسردگی عمده که به یک نوبت دوره‌ی درمانی پاسخ نداده است.	۱- افکار خودکشی و خطر اقدام به خودکشی ۲- مصرف داروهای پایین‌آورنده آستانه تشنج ۳- سابقه تشنج در فرد یا خانواده او ٤- وجود علایم سایکوتیک حاد ٥- بارداری(کنتراندیکاسیون نسبی) ٦- کودکان ۷- وجود اشیای فلزی در بدن	کلینیک سرپایی	۱۵ جلسه	۵ جلسه در هفته، در سه هفته	۱۵ تا ٤٠ دقیقه	

- تاریخ اعتبار این راهنما از زمان ابلاغ به مدت سه سال است و پس از آن باید به‌روزرسانی شود.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Facilities Conducting rTMS Treatment as of November 1, 2014

The Jikei University Hospital (Minato-Ku, Tokyo)
The Jikei University Daisan Hospital (Komae, Tokyo)
Shimizu Hospital, The Kyosaikai Medical Foundation (Kurayoshi, Tottori)
Tokyo General Hospital, The Kenkoukai Medical Foundation (Nakano-Ku, Tokyo)
Nishi-Hiroshima Rehabilitation Hospital, The Houwakai Medical Corporation (Hiroshima, Hiroshima)
Kimura Hospital, The Jujinkai Medical Corporation (Sabae, Fukui)
Kyoto Ohara Memorial Hospital, The Koryokai Medical Corporation (Kyoto, Kyoto)
Hakodate Shintoshi Hospital, The Yushinkai Medical Association (Hakodate, Hokkaido)
Kousei Hospital, The Corporate Medical Association Rokushinkai (Kobe, Hyogo)
Izumi Memorial Hospital, The Izenkai (Adachi-Ku, Tokyo)
Shin-Yurigaoka General Hospital, The Sanseikai (Kawasaki, Kanagawa)

(Upper limb hemiparesis)　(Aphasia)
(Dysphagia)　(Lower limb hemiparesis)

- Out of the 11 facilities mentioned above, the Jikei University Hospital and Shimizu Hospital treat “upper limb hemiparesis” and “aphasia.”
- The Jikei University Daisan Hospital treats “upper limb hemiparesis,” “aphasia,” “dysphagia” and “lower limb hemiparesis.”
- The other eight facilities only treat “upper limb hemiparesis.”

Introduction

In 1998, while studying at the Karolinska Institutet, I was blessed with the opportunity to use a magnetic stimulation device. I was surprised at how easily cerebral cortex could be stimulated with this device, and I still remember, as if it had been yesterday, the "tremor of excitement" that I felt when imagining that some day this magnetic stimulation device would contribute to the development of new therapies in the field of rehabilitation. For the clinical application of magnetic stimulation therapy, I first repeatedly conducted basic experiments using rat models of brain injury and stopped these temporarily after gaining first insights. Then, aiming to challenge the notion accepted worldwide that neurological sequelae of stroke will not improve in the chronic stage, to help patients who suffer from the neurological sequelae of stroke, and to further develop rehabilitation medicine, I made a point of calling on Dr. Wataru Kakuda, one of the authors and editors of this book, to return from Stanford University, and eventually in April 2008 we began to conduct NEURO therapy.

In *Treatment Approaches for the Recovery of Fine Motor Functions of the Hand and Finger by Use of rTMS and Intensive Occupational Therapy – Latest Rehabilitation Methods for the Treatment of Post-stroke Upper Limb Hemiparesis* (Miwa-Shoten Ltd.), which was published in July 2010, we introduced "NEURO" (a treatment protocol using rTMS treatment in combination with intensive rehabilitation), which our department developed and promoted for the first time in the world. In particular, during the last few years this NEURO therapy has been widely featured in the media, such as on TV, and an unending stream of patients have visited our department. To date more than 3000 patients with neurological sequelae of stroke, not only from throughout Japan but also from abroad, have visited our outpatient department. As a result, the number of patients who have undergone NEURO therapy has increased rapidly, and as of October 2014, in total more than 2000 patients have received the therapy at 13 affiliated and collaborative hospitals throughout Japan.

This book is a practical guide on "rTMS treatment and rehabilitation for the treatment of neurological sequelae of stroke." We have found that rTMS in combination with rehabilitation is useful not only for the treatment of poststroke upper

limb hemiparesis but also for the treatment of other neurological sequelae of stroke, namely, aphasia, dysphagia, and lower limb hemiparesis and have published many research papers on this topic in international journals. Research resulted in as many as 14 research papers on the use of rTMS for the treatment of the neurological sequelae of stroke that can be accessed on PubMed (from 2010 to October 2014). Thus, it is no exaggeration to say that this book was written based on clinical data obtained from cases that we were involved in ourselves.

Since magnetic stimulation devices are currently approved for testing and not as therapeutic equipment, magnetic stimulation therapies such as NEURO are conducted based on the approval of the ethics committee of each institution that we collaborate with. Until recently, it was recommended that the upper limit of magnetic stimulation pulses should be 5000 pulses per week. However, according to the "Recommendations for Transcranial Magnetic Stimulation (TMS)" by the Committee on Brain Stimulation Methods of the Japanese Society of Clinical Neurophysiology (JSCN) in the *Japanese Journal for Clinical Neurophysiology* Vol. 40, No. 1, 2012, the upper limit of magnetic stimulation should be up to 15,000 pulses per week. Accordingly, magnetic stimulation conducted as in the case of NEURO therapy, which involves low-frequency stimulation with 14,400 pulses per week, is within the range of the upper limit recommended by the JSCN.

Finally, I want to express my gratitude to all members of the 13 hospitals who have banded together in the same spirit and cooperated in this clinical project. I hope that this book will be used by patients who suffer from neurological sequelae of stroke and their families and will serve as a reference for TMS treatment, which is one of a number of approaches to therapeutic rehabilitation.

October, 2014 Masahiro Abo

Chapter 1
rTMS and Its Potential Use in Stroke Rehabilitation

1 The Principle Behind TMS

The first report on the application of transcranial magnetic stimulation (TMS) as a new cerebral cortex stimulation technique that can be used as an alternative to direct electrical stimulation in humans was published in *the Lancet* in 1985. Barker [1] succeeded in painless recording of motor evoked potentials (MEPs) from the muscles of the hand and finger by transcranially applying a magnetic field, generated by an electric current passing through a circular coil, over the primary motor area of the cerebral cortex.

TMS consists of the TMS device main unit and a stimulation coil that is connected thereto (p. 119). The stimulation parameters (e.g., frequency, intensity, train duration) are set on the TMS device main unit, and TMS is conducted by applying the stimulation coil to the surface of the skull. Recently, there are also TMS devices with a cooling system that prevent an increase in the temperature of the coil, thus enabling prolonged continuous stimulation.

The principle by which the cerebral cortex is stimulated by TMS is based on the famous Faraday's law on electromagnetic induction. As shown in Fig. 1.1, when an electric current flows within a circular coil, a magnetic field (magnetic flux) is generated perpendicular to the plane of the coil and reaches the cerebral cortex after passing through soft tissues and the skull. To generate such a magnetic field, it is important that the electric current flowing through the coil is not a steady-state current but constantly changes its velocity.

In fact, the more rapidly the electric current flows, the greater becomes the magnetic field that is generated. The magnetic field that reaches the cerebral cortex generates an eddy current that is perpendicular to this magnetic field, and thus parallel to the plane of the coil (skull). The direction of the eddy current that is generated here is opposite to the direction of the electric current that flows through the coil. This eddy current acts on interneurons (that flow parallel to the skull) located in the cerebral cortex, and eventually also affects neurons throughout the brain stem and

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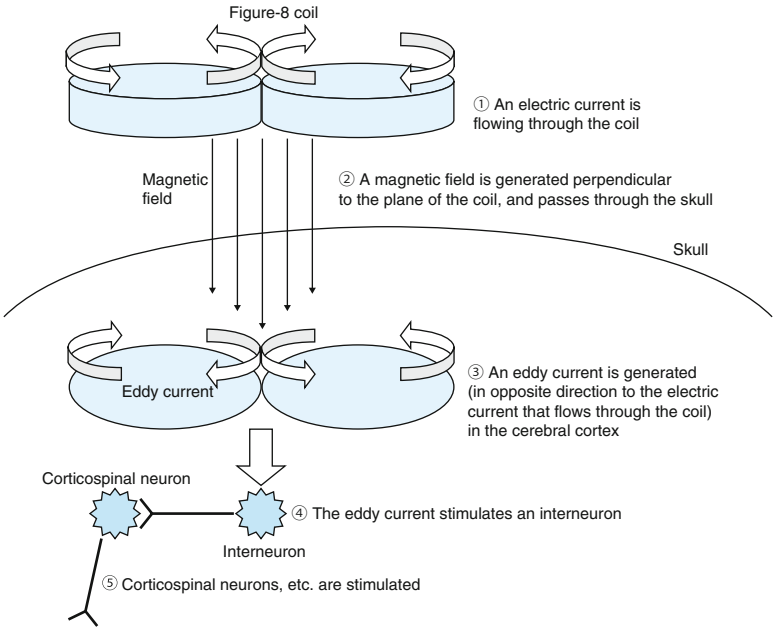

Fig. 1.1 Mechanism through which TMS stimulates the cerebral cortex

spinal cord that descend from the cerebral cortex. Thus, evidently TMS results in "transcranial" magnetic stimulation, but what actually affects the neurons is the eddy current that is generated in vivo by "magnetic stimulation."

The magnetic stimulation waves that are produced by TMS can be monophasic or biphasic waveforms. The biggest difference between these two kinds of waveforms is the number of neurons that are stimulated. More specifically, in the case of biphasic stimulation, which causes the electric current that flows through the coil to become bidirectional, more neurons are stimulated, and this stimulus reaches over a wider area than in case of monophasic stimulation. Regarding these differences, monophasic stimulation is considered appropriate for examinations in which MEPs, etc. are induced, and biphasic stimulation, which has a greater impact on the cerebral cortex, is considered to be more appropriate for therapeutic purposes such as described later.

The electric current that flows through the coil generates a magnetic field, which in turn generates an eddy current in vivo that flows in opposite direction to the electric current that is generated by the coil. Then interneurons are stimulated by this eddy current.

Schematic representation of the magnetic fields that are generated by these two types of stimulation coils (the higher the area is located, the greater is the magnetic field that is generated). While in the case of the circular coil the magnetic field at the center of the loop becomes almost zero (in this figure represented as "a hollow"), in case of the figure-8 coil the maximum magnetic field is in the center of the coil (at the intersection of the two loops) (in this figure represented as "a peak").

There are two types of TMS stimulation coils that are typically used, circular coils and figure-8 coils (Fig. 1.2). As shown in Fig. 1.3 there are differences in the distribution of the magnetic field that is generated by these two types of coils. First, when using a circular coil the highest magnetic field is generated beneath the coil loop, and the magnetic field beneath the center of the coil becomes zero. Therefore, circular coils are suitable for the indefinite stimulation of a wide area of the cerebral cortex; however, circular coils are by no means suitable for the local stimulation of narrow sites of the cerebral cortex, regardless of whether TMS is used for examinations or therapeutic purposes. In contrast, when using a figure-8 coil the two eddy currents that are generated by magnetic stimulation at the intersection of its two loops overlap, and the strongest magnetic field is generated locally. Therefore, when conducting TMS

Fig. 1.2 Circular coil and figure-8 coil were both manufactured by MagVenture

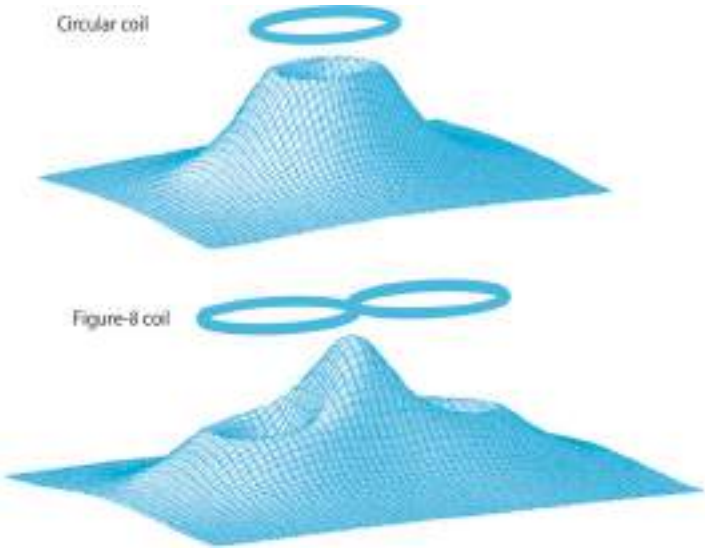

Fig. 1.3 Differences in the magnetic fields that are generated by these two types of coils

stimulation through which this intersection overlaps with the target area of the cerebral cortex, different from when using a circular coil, it becomes possible to stimulate an extremely limited area. Generally, the spatial resolution of figure-8 coils is considered to be within 5 mm, and at this intersection a magnetic force is generated that is several times higher than that at other sites of the coil. For this reason, at present TMS is considered an innovative device with which the cerebral cortex can be stimulated locally with high spatial resolution and without causing pain.

2 High-Frequency rTMS and Low-Frequency rTMS

As reported by Barker [1], initially TMS was used for physiological tests with the primary purpose to determine MEPs of peripheral muscles. However, hereafter with regard to repetitive transcranial magnetic stimulation (rTMS), it has been found that continuous application of TMS stimulation caused local changes to neural activity in the cortex. More specifically, it became clear that the application of rTMS stimulation affects brain "plasticity."

More specifically, besides the stimulation site, the following three factors serve as determinant parameters for the effect of rTMS on the cerebral cortex, and among these in particular the applied frequency plays an important role:

(i) Frequency of pulses (number of pulses per 1 second that are applied, expressed in Hz)
(ii) Intensity of pulses [expressed as the percentage (%) of the motor threshold (MT) (the minimum stimulus intensity that can induce muscle activity)]
(iii) Train duration (number of pulses that are applied)

This is because it has been confirmed that the effects of rTMS on the cerebral cortex greatly differ depending on the frequency of pulses. Generally, rTMS that is performed at a frequency of 5 Hz or higher is called high-frequency rTMS, and rTMS that is performed at a frequency of lower than 1 Hz is called low-frequency rTMS. However, in conclusion it has been found that while high-frequency rTMS enhances local neural activity of the stimulated site, low-frequency rTMS suppresses local neural activity at the stimulated site. Namely, the effects of rTMS on the cerebral cortex are completely opposite depending on the frequency used.

There are a number of reports that high-frequency rTMS enhances local neural activity of the cerebral cortex, including by Pascual-Leone et al. [2], who found that the amplitude of MEPs induced by primary motor area stimulation by use of the same stimulus intensity increased for approximately 3 minutes after applying a 10-pulse rTMS train at 20 Hz and 150 % of MT (train duration 0.5 seconds) to the primary motor area of the cerebral cortex (this was interpreted to mean that stimuli of the same intensity produced enhanced activity and excitability of the primary motor area of the cerebral cortex if they induced an increase in MEP amplitude). Similarly, Wu et al. [3] stated that the amplitude of MEP induced after applying a 30-pulse rTMS train at 15 Hz and 120 % MT (train duration 2 seconds) increased for 90 seconds. Moreover,

an example in which stimuli below the motor threshold were used is, e.g., a report by Maeda et al. [4], who found that the size of MEP was amplified for 2 minutes after applying a 240-pulse rTMS train at 20 Hz and 90 % MT (train duration 12 seconds). They also pointed out that alteration of the local activity of the cerebral cortex with stimuli below the motor threshold requires prolonged stimulation.

In contrast, there are well-known reports, such as by Chen et al. [5] and Maeda et al. [6], that low-frequency rTMS suppresses local neural activity of the cerebral cortex. According to Chen et al. [5], after applying low-frequency rTMS, namely, a 810-pulse rTMS train at 0.9 Hz and 115 % of MT (train duration 15 minutes) to the primary motor area of the cerebral cortex, the MT of the stimulated side increased for 15 minutes and longer after stimulation (because it becomes difficult to receive a response to stimuli of the same intensity), and the amplitude of the induced MEPs decreased. Moreover, Maeda et al. [6] stated that MEPs decreased for 2 minutes when applying low-frequency rTMS, namely, a 240-pulse rTMS train at 1 Hz and 90 % of MT (train duration 4 minutes) only to one side of the primary motor area.

3 Neuromodulatory Mechanisms of rTMS

It is believed that the effects of rTMS on the local excitability of the cerebral cortex, more specifically, the mechanisms that underlie the neuromodulatory effects of rTMS, are alterations in synaptic efficiency (influence on synaptic signaling), which are the basis of brain plasticity. An increase in synaptic efficiency is called long-term potentiation (LTP), and a decrease in synaptic efficiency is called long-term depression (LTD). Conversely one can say that high-frequency rTMS induces LTP and low-frequency rTMS induces LTD.

According to the results of animal studies, LTP/LTD induction by rTMS appears to be mediated by neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA). For instance, it has been confirmed in animal studies that inhibition of the glutamate-binding site on *N*-methyl-D-aspartate (NMDA) receptors by administrating NMDA receptor antagonists such as dextromethorphan or memantine reduces LTP/LTD induction resulting from rTMS [7, 8]. On the contrary, it has been reported that LTP/LTD induction resulting from rTMS is promoted when inhibiting inhibitory systems that are mediated by GABA [9]. This may be interpreted as meaning that while activation of the glutamate system enhances brain plasticity, activation of the GABA system decreases brain plasticity.

Since it has already been confirmed that brain plasticity is affected by various factors, it is conceivable that the degree of the neuromodulatory effect that is achieved by rTMS also undergoes similar effects. For instance, the blood levels of certain hormones appear to affect brain plasticity. Inghilleri et al. [10] examined the impact of the menstrual cycle on the effect of high-frequency rTMS in eight women. As a result, on Day 1 of the menstrual cycle no significant increase in the size of MEP was observed when applying high-frequency rTMS (5 Hz) to the primary motor area. However, on Day 14 of the menstrual cycle a significant increase in the size of MEP was observed when

applying the same treatment. Based on this result, it was concluded that blood estrogen levels significantly affect the efficacy of high-frequency rTMS (along with increases in blood estrogen levels, brain plasticity, as well as the efficacy of rTMS increase).

Moreover, Sale et al. [11] investigated whether there are diurnal variations in the effects of paired-associative stimulation (PAS) consisting of peripheral nerve stimulation paired with rTMS on the primary motor area in 20 adults. As a result, a significant increase in the size of MEPs was observed both when PAS was conducted in the morning or afternoon, but the degree of increase was greater when PAS was conducted in the afternoon than when it was conducted in the morning. This result was interpreted to mean that there is a possibility that the blood levels of hormones that are closely related to the circadian rhythm such as melatonin and cortisol affect brain plasticity.

Moreover, brain plasticity has also been reported to be affected by certain genetic predispositions. After Kleim et al. [12] had suggested due to differences observed in the response to exercise therapy that brain-derived neurotrophic factor polymorphism (BDNF val66met polymorphism) affects brain plasticity, Cheeran et al. [13] examined the influence of BDNF polymorphisms on the effect of theta burst stimulation (TBS) (p. 164). When comparing the stimulatory and inhibitory effects of TBS in the group without the polymorphism [Val/Val type, where the nucleotides at codon 66 were both valine] and the group with the polymorphism [Val/Met type, where one of the nucleotides at codon 66 had mutated to methionine, or Met/Met type, where both nucleotides at codon 66 had mutated to methionine], it was found that in the group with polymorphism neither a sufficiently stimulatory nor inhibitory effect was exhibited, while in the group with no polymorphism significant changes were observed.

Therefore, for the therapeutic use of rTMS it is necessary to correctly identify under which circumstances brain plasticity increases, namely, whether the neuromodulatory effect of rTMS will be amplified or whether conversely plasticity will be reduced (namely, whether the effects of rTMS will be attenuated).

4 rTMS and Rehabilitation

It is believed that the so-called brain reorganization and restoration of impaired neuronal functions requires the functional and subsequent structural reorganization of the compensatory functional site as shown in Fig. 1.4, and the first step of this process can be interpreted as LTP/LTD induction.

For this reason the neuromodulatory effect of rTMS is undoubtedly expected to promote the “first step of brain reorganization.” However, given the short duration of this effect, one can infer that the effect of rTMS is not sufficient to induce structural reorganization in a subsequent step. Accordingly, one can say for sure that rTMS increases brain plasticity; however, it is possible that the application of rTMS alone is not sufficient for achieving a long-lasting brain reorganization (in particular structural reorganization).

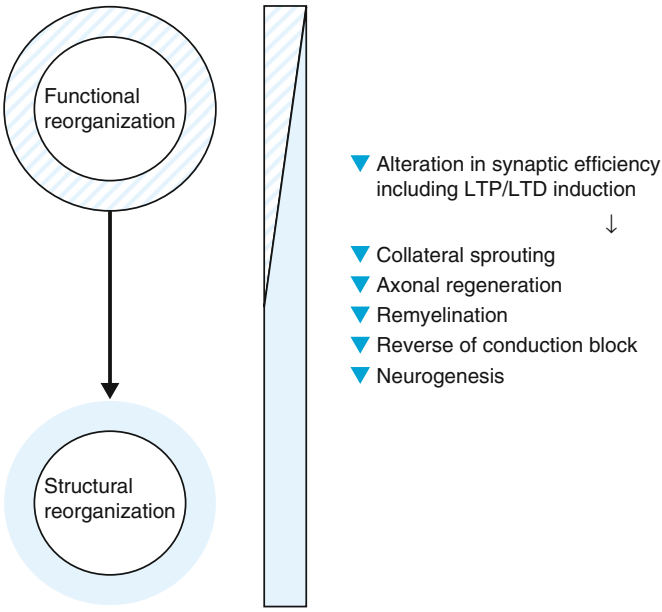

Fig. 1.4 Functional and structural reorganization in the restoration of neuronal functions. LTP/LTD induction is the first step of the reorganization of the brain when restoring neuronal function

Therefore, we thought that by combining rTMS with conventional rehabilitation it might be possible to clinically introduce rTMS as a therapeutic intervention for neurological sequelae of stroke that promotes the brain reorganization. In short, we thought that rTMS could take in the position of a preconditioning method that increases brain plasticity and that it would be optimal to combine rTMS with intensive rehabilitation. As a result, the concept of "rTMS and intensive rehabilitation combination therapy" described later became a fundamental idea that has yielded many favorable treatment outcomes. The combination of rTMS and intensive rehabilitation enhances the beneficial effect of each intervention procedure, and therefore this innovative therapy approach is increasingly used in clinical practice.

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Chapter 2
rTMS for Upper Limb Hemiparesis after Stroke

1 Pathology and Current Status of the Treatment

A. Current Status of Rehabilitation in Poststroke Upper Limb Hemiparesis

The mortality rate from stroke has been declining with the development of drug therapies in the acute phase and the established EBM for the treatment. Referring to the details of the "Japanese Guidelines for the Management of Stroke 2009," a rehabilitative intervention from the early stage after stroke onset is recommended as "Grade A" in the item of rehabilitation of motor disorders and activities of daily living (ADL) disability. Therefore, it is considered essential to perform consistent rehabilitation from the acute phase in stroke treatment (Table 2.1) [1]. However, in rehabilitation for motor disorders and ADL, facilitations (neuromuscular facilitation procedures) [including the Bobath method, neurodevelopmental exercise (Davis), proprioceptive neuromuscular facilitation (PNF) method, and the Brunnstrom method] are classified as Grade C. In addition, in the item of rehabilitation of upper limb dysfunction in the guidelines, repetitive motion exercise, goal-oriented exercise, and constraint-induced movement (CI) therapy, which suppresses the movement of the unaffected upper limb, are considered useful, as shown in Table 2.2 [1]. These facts have been demonstrated also in the rehabilitation of poststroke upper limb hemiparesis published in the Lancet, described below [2].

B. Functional Recovery of Poststroke Upper Limb Hemiparesis

As described above, it is considered that the number of patients with severe upper limb hemiparesis has been declining with the introduction of rehabilitation from the acute phase. However, relatively few stroke patients became able to use their

M. Abo, W. Kakuda, *Rehabilitation with rTMS*,
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Table 2.1 Rehabilitation of motor disorders and ADL

1. For neurological sequelae of stroke, it is strongly recommended to actively perform rehabilitation from an early stage in order to facilitate the recovery of dysfunction and decreased function (Grade A)
2. For patients in the early stage after stroke onset, it is recommended to increase the frequency and amount of training in order to facilitate the recovery of decreased function more effectively (Grade A)
3. Facilitations (neuromuscular facilitation procedures) [including Bobath method, neurodevelopmental exercise (Davis), proprioceptive neuro-muscular facilitation (PNF) method and Brunnstrom method] can be performed; however, there is no scientific evidence that shows these methods are more effective than traditional rehabilitation (Grade C1)

Excerpt from Ref. [1]

Table 2.2 Rehabilitation of upper limb dysfunction

1. For the upper limb on the paralyzed side, it is strongly recommended to actively repeat a specific training (including reach exercise of the upper limb on the paralyzed side, repetitive exercise of both upper limbs along with a metronome, goal-oriented exercise, and image training) (Grade A)
2. For patients with mild paralysis, it is recommended to administer a treatment by suppressing the movement of the upper limb on the non-paralyzed side and forcing the patient to use the upper limb on the paralyzed side in daily life, provide d that the indication is properly selected (Grade B)
3. For moderately paralyzed muscles, in particular for strengthening the wrist dorsiflexor muscle, electrical stimulation is recommended (Grade B)

Reprinted from Ref. [1]

paralyzed upper limb as a functional hand after rehabilitation. In a previous report on the functional prognosis in patients with poststroke upper limb hemiparesis, Duncan et al. [3] reported that significant improvement can be observed within 1 month of the stroke onset and most patients reach a plateau state by 6 months after the stroke onset (Fig. 2.1). In addition, Jorgensen et al. [4] reported that patients with mild, moderate, and severe upper limb hemiparesis reach a plateau state in 6 weeks, 10 weeks, and 15 weeks after the stroke onset, respectively. Most patients with poststroke upper limb hemiparesis undergo an evaluation of the functional prognosis of their paralyzed hand, based on which they receive rehabilitation to acquire the ADL necessary for them. For example, patients with mild paralysis mainly receive dexterity training such as chopsticks operation, handwriting, and cup retention.

In moderate to severe cases, a patient changes hand dominance or performs using one hand movements that had previously been performed with both hands. In other words, a “compensatory approach” is generally adopted in many cases in the general rehabilitation from the recovery to maintenance phase.

However, findings on poststroke cerebral plasticity in recent years show that there is some plasticity even in the chronic stage of stroke patients after some time has elapsed from the onset. For example, CI therapy, which intensively approaches

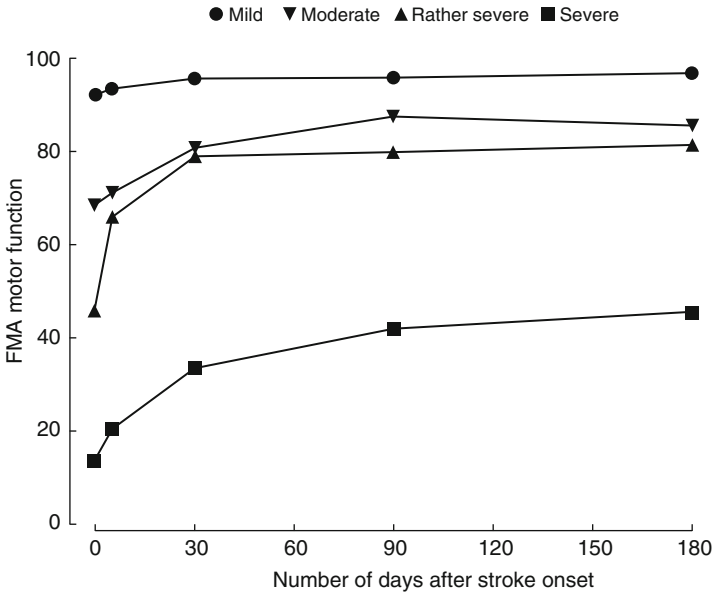

Fig. 2.1 Changes in post-stroke upper limb hemiparesis score. After the stroke onset, the FMA score of upper limb hemiparesis reaches a plateau state on Day 90 regardless of the severity (Adopted from Ref. [3])

the upper limb on the paralyzed side, is one of the neurorehabilitations (hereinafter, NR) widely performed in chronic stroke patients. Previous reports on brain functional reorganization in CI therapy indicated that improvement of the upper limb on the paralyzed side is related to the expansion of the neural plastic area of the lesional hemisphere and that it could influence on the interhemispheric balance [5, 6]. Thus, it is now considered that there is a possibility of maximizing the upper limb function by influencing the cerebral plasticity even in patients with poststroke upper limb hemiparesis who were previously believed to have reached a functional plateau. In this context, another type of "rehabilitation approach for functional recovery" is beginning to attract attention.

In the systematic review of poststroke rehabilitation published by Langhorne et al. [2] in 2009, the results of randomized controlled trials (RCTs) of rehabilitation training for a variety of strokes in the past were statistically analyzed. According to this report, 88 studies (total of 2687 patients) of upper limb training and 37 studies (total of 1467 patients) of hand-finger training were identified. In the upper limb training, CI therapy, myoelectric feedback, electrical stimulation therapy, and robot training are reported to be highly effective. On the other hand, in finger training, the results showed that a sufficient effect cannot be obtained even after the same training as that for upper limb cases was performed. Under these circumstances, repetitive transcranial magnetic stimulation (rTMS) has recently started attracting attention as an NR method.

C. Current Status of rTMS

rTMS is an up-and-coming treatment method, which is applied to bring out the potential of the brain reorganization by directly stimulating the cerebral cortex. As an EBM for rTMS, a meta-analysis of rTMS treatment for stroke patients was reported in 2012 [7].

In this report, 18 articles published from 2005 through 2011 were reviewed (in 5 of the articles, two stimulation approaches were applied), where rTMS was performed in a total of 392 patients. Looking at the details, they varied in terms of the time from the onset to the intervention. Three articles focused on the acute phase, another three focused on the subacute phase, seven articles focused on the chronic phase, and the remaining articles dealt with various phases. With respect to the lesions, 6 articles covered subcortical lesions, and 11 articles covered both subcortical and cortical lesions (the remaining 1 article compared subcortical and cortical lesions). With respect to the stimulation method, the following methods were applied: a low-frequency rTMS to the unaffected hemisphere in eight studies, a high-frequency rTMS to the affected hemisphere in five studies, a low-frequency rTMS to the affected hemisphere in one study, both low-frequency rTMS to the unaffected hemisphere and high-frequency rTMS to the affected hemisphere in two studies, and theta burst stimulation (TBS) (p. 164) in the remaining two studies.

Of the 392 patients studied in 18 articles, adverse effects were observed in 4 patients, in whom headache and fatigue occurred, but no serious convulsive seizure was reported. As a consequence, the effect size was 0.55 when all the articles were collectively analyzed. When comparing the low-frequency and the high-frequency rTMS in the subgroup analysis, the effect size was 0.69 and 0.41, respectively, which means that low-frequency rTMS is superior. According to the lesions, the results showed that the effect size of subcortical lesions was 0.73 and that of the other lesions was 0.45. That is, rTMS is more effective in patients with subcortical lesions.

From these results, rTMS is believed to bring significant improvements in poststroke upper limb hemiparesis and is expected to produce a greater effect through performing the treatment in accordance with the stimulation method, lesions, and intervention time.

Thus, we found that rTMS is effective for poststroke upper limb hemiparesis and particularly significant effects can be obtained when low-frequency rTMS is performed on the unaffected hemisphere during the chronic phase. The detailed protocol and treatment outcome of our ongoing study, “NEURO-15 (NovEl intervention Using Repetitive TMS and intensive Occupational therapy-15 days protocol),” will be described below. This protocol began to be implemented in April 2009 after a process of trial and error, and ongoing studies are being carried out based on the same philosophy and protocol at nine institutions throughout Japan. The total number of patients receiving NEURO was more than 2000 as of October 2014. Not only the number of patients who experienced the therapy but also results as well are unprecedented in Japan.

2 Protocol of the Combination Treatment of Low-Frequency rTMS and Intensive Occupational Therapy

A. Overview of NEURO-15

1) Eligibility Criteria

The major eligibility criteria of NEURO-15 are set as shown in Table 2.3, based on not only the contraindications and precautions published in the previous guidelines of rTMS treatment that Wassermann [8] proposed (Wassermann Guidelines) but also the eligibility criteria of CI therapy [9] which have been traditionally proposed. Today, these are used as common criteria for all institutions.

2) Details of rTMS Treatment

Low-frequency rTMS is applied using MagPro R30 and a figure-8 coil (both are manufactured by Magventure A/S). The stimulation site for low-frequency rTMS is the primary motor hand and finger area of the nonlesional hemisphere; that is, the optimal site of stimulation defined as the location where the largest motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the unaffected upper limb was elicited on electromyography (Fig. 2.2). The intensity of stimulation is set at 90 % of the motor threshold (the minimum stimulus intensity that can produce MEP at the stimulation site), and a low-frequency rTMS of 1 Hz is applied to the unaffected hemisphere for 20 minutes (a total of 1200 pulses) per session (Table 2.4). In principle, the patient must be attended by a physician during

Table 2.3 Eligibility criteria of NEURO-15

1. BRS for hand-fingers on the paralyzed side of 3–5. (At least, the hand and finger can be actively flexed without any problems. However it does not matter whether or not the patient can perform isolated movement when determining eligibility)
2. Age (at the time of determining the eligibility) between 18 and 90 years
3. Time between onset and intervention of more than 12 months
4. History of a single stroke only (no bilateral cerebrovascular lesion)
5. No significant cognitive impairment (preferably a Mini Mental State Examination score of more than 26)
6. No active systemic or mental illness requiring medical management
7. No recent history of seizure for at least one year preceding the intervention
8. No abnormal wave form, such as epileptic discharge on electroencephalogram (electroencephalogram as a screening test is performed only in patients with a history of seizures and in patients receiving an oral anti-epileptic drug)
9. No contraindications listed in the guidelines proposed by Wassermann (such as the presence of intracranial metal objects, the presence of a cardiac pacemaker, and pregnancy)

As of December 2012

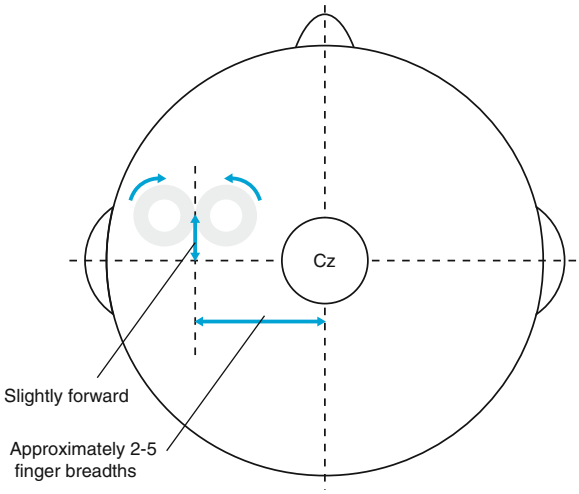

Fig. 2.2 Stimulation site for low frequency rTMS. Stimulate the motor center for the hand and finger which is located about 2–5 finger breadths away from Cz (vertex) based on the international 10–20 method, and slightly forward

Table 2.4 An example of rTMS treatment in NEURO-15[a]

Coil used	Figure-8 coil
Site	Non-lesional hemisphere (prim. motor hand and finger area)
Intensity	90 % of motor threshold
Frequency	Low-frequency rTMS (1 Hz)
Duration	1 session lasting 20 minutes (1200 pulses), once or twice daily
Days in hosp.	15 days

[a]The actual treatment is adjusted by each institution (As of December 2012)

stimulation. As a matter of our policy, the treatment should be immediately discontinued when adverse events (e.g., convulsion, headache, and discomfort of stimulation site) or other neurological symptoms occur.

3) Treatment Schedule

NEURO-15 is a therapeutic intervention that is performed during hospitalization, in principle. Table 2.5 shows an example of a training schedule during hospitalization. Over the course of a 15-day hospitalization, a treatment session consisting of low-frequency rTMS over the nonlesional hemisphere and intensive occupational therapy (OT) is performed twice daily in principle (except Sundays). Prior to applying NEURO-15, we make it a rule to obtain the consent of each study patient after providing them with sufficient information about the treatment.

Table 2.5 An example hospitalization schedule of NEURO-15[a]

Fri.	Saturday	Sun.	Monday to Saturday	Sun.	Monday-Tuesday	Wednesday
Evaluation at admission	Low-frequency rTMS (20 minutes)	No treatment	Low-frequency rTMS (20 minutes)	No treatment	Low-frequency rTMS (20 minutes)	
	One-to-one training (60 minutes)		One-to-one training (60 minutes)		One-to-one training (60 minutes)	
	Self-exercise (60 minutes)		Self-exercise (60 minutes)		Self-exercise (60 minutes)	
Low-frequency rTMS (20 minutes)			Low-frequency rTMS (20 minutes)		Low-frequency rTMS (20 minutes)	Evaluation at discharge
One-to-one training (60 minutes)			One-to-one training (60 minutes)		One-to-one training (60 minutes)	
Self-exercise (60 minutes)			Self-exercise (60 minutes)		Self-exercise (60 minutes)	

[a]An example of being hospitalized on a Thursday. The actual hospitalization schedule is adjusted by each institution (As of December 2012)

B. OT Evaluation in NEURO-15

At the time of admission and discharge, (1) the upper limb function on the paralyzed side and (2) the usage of the paralyzed side in daily life are evaluated.

1) Evaluation of Upper Limb Function

The evaluations of upper limb function conducted in NEURO-15 are as follows:

(i) Brunnstrom recovery stage (BRS)
(ii) Ueda's 12-grade motor function test for hemiplegia
(iii) Fugl-Meyer assessment (FMA)
(iv) Wolf motor function test (WMFT)
(v) Modified Ashworth scale (MAS)
(vi) Simple test for evaluating hand function (STEF)
(vii) Ten second test
(viii) Grip strength
(ix) Range of motion (ROM)
(x) Sensory examination
(xi) Action research arm test (ARAT)

BRS is a method to clinically classify the recovery process of paralysis caused by central nervous system injury by focusing on synergies (Table 2.6) [10]. It is classified into six stages from I to VI, which qualitatively evaluate a series of recovery processes: first, the flaccid state in the acute phase is observed, associative reactions and synergies appear, individual movements can be observed, and normal movements gradually return with the attenuation of spasticity. However, patients with paralysis do not uniformly follow this recovery process and may stop recovering at a certain stage according to the lesion. In Japan, BRS is widely used as the most basic and common qualitative functional evaluation method of central motor paralysis. However, it has some disadvantages: the range varies by each stage, and the stages are not classified in a detailed manner. Thus, this is mainly used as a screening tool.

FMA is a scale suitable to comprehensively evaluate the recovery of motor function. It enables us not only to determine the motor function of the upper and lower limbs by focusing on the synergy pattern but also to evaluate the balance, sensation, ROM, and other aspects (Table 2.7) [11]. In the study patients of NEURO-15, we use 33 items selected from FMA, which are related to the upper limb function such

Table 2.6 Brunnstrom recovery stage (upper limb, hand and finger)

Stage	Upper limb	Hand and finger
I	Flaccid. No voluntary movement	Flaccid
II	Voluntary elevation, retraction, abduction, external rotation, and extension of the shoulder, and voluntary flexion and supination of the elbow can be slightly or partly observed	Voluntary finger flexion is almost impossible
III	(a) Volitional flexion within synergies described in Stage II can be partly done voluntarily (b) In addition, volitional extension within synergies, including depression, protrusion, adduction, internal rotation and flexion of the shoulder, and extension and pronation of the elbow can be done voluntarily	Mass flexion can be done, but mass extension cannot be done Voluntary finger extension cannot be done, but reflexive extension can be done
IV	(a) Can stretch the arm forward (b) Can pronate and supinate with keeping the elbow close to the side and flexing it at 90 degrees (c) Can roll the arm back and touch the waist	A lateral side pinch can be done and release by moving the thumb also can be done Voluntary finger flexion can be done slightly
V	(a) Can stretch the arm forward and elevate it higher than Stage IV (b) Can stretch the arm to the side (c) Can pronate and supinate the forearm with the elbow at the extended position	Finger grip, cylinder grip and ball grip can be done. Can spread all the fingers and the thumb
VI	Can perform the isolated movements described in Stage V quickly, easily and coordinately Normal movements returned or almost returned	All kinds of grips can be done well. Voluntary finger extension can be done over the entire range of motion Individual movements of the finger also can be done

Reprinted from Ref. [10]

Table 2.7 Fugl-Meyer assessment [1. Motor function and balance (upper limb)]

Evaluation item				Score		
AA shoulder/elbow/forearm (subtotal/36 points)				None	Sufficient	Insufficient
I. Reflex		Biceps and finger flexor		0		2
		Triceps		0		2
II. Volitional movement within synergies	(a) Flexor[a]	Shoulder	Retraction		1	2
			Elevation	0	1	2
			Abduction	0	1	2:>90°
			External rotation	0	1	2
		Elbow	Flexion		1	2
		Forearm	Supination	0	1	2
	(b) Extensor[b]	Shoulder	Adduction/internal rotation	0	1	2
		Elbow	Extension		1	2
		Forearm	Pronation	0	1	2
III. Volitional movement mixing synergies (flexor/extensor)		Move the arm around to the lumbar spine in a sitting posture		0	1: Just beyond anterior superior iliac spine	2
		Shoulder flexion at 90° with elbow in an extended position and the forearm in an intermediary position		0	1: The elbow flexes at a later stage	2
		Pronation and supination with the shoulder at 0° and the elbow flexed at 90°		0	1	2

(continued)

Table 2.7 (continued)

Evaluation item			Score		
IV. Volitional movement with little or no synergies	Shoulder abduction at 90° with elbow at an extended position and forearm at a pronated position in a sitting posture		0	1: The elbow flexes and the forearm supinates during the process	2
	Shoulder flexion at 180° with the elbow at an extended position		0	1: The elbow flexes at a later stage	2
	Pronation and supination with elbow at an extended position and with shoulder at a flexed position at 30 to 90°		0	1	2
V. Normal reflex activity[c]	Examine the tendon jerks of I		0	1: >1 increased reflex response, >2 mild increased reflex responses	2
B. Wrist joint[d] (subtotal/10 points)			None	Sufficient	Insufficient
Keep the dorsiflexion in the wrist joint at 15° with the shoulder at 0° and the elbow flexion at 90°			0	1: Can be performed if no resistance is applied	2: Can be performed even if gentle resistance is applied
Volar flexion/dorsiflexion in the wrist joint			0	1	2: Can be performed over the whole range of motion
With the shoulder in a slightly flexed and abducted position the elbow in an extended position, and the forearm in a pronated position	Keep the dorsiflexion in the wrist joint at 15°			1: Can be performed if no resistance is applied	2: Can be performed even if gentle resistance is applied
	Repeated volar flexion/dorsiflexion in the wrist joint		0	1	2: Can be performed over the whole range of motion
	Circumduction		0	1	2: Can be smoothly performed and have sufficient range of motion
C. Finger[e] (subtotal/14 points)			None	Sufficient	Insufficient
Mass flexion			0	1	2
Mass extension			0	1	2
Grasp	(a) Digit 2–5 extension in MCP, flexion in PIP and DIP		0	1: Weak	2: Can be performed even if strong resistance is applied

	(b) Pinch a piece of paper using the index finger's MP joint and the thumb at the extended position	0	1: The paper can be pulled out by weak force	2: The paper cannot be pulled out
	(c) Pinch a pencil using the pads of the thumb and the index finger	0	1: The paper can be pulled out by weak force	2: The paper cannot be pulled out
	(d) Cylinder grip	0	1: The paper can be pulled out by weak force	2: The paper cannot be pulled out
	(e) Grip a tennis ball with the thumb at the opposed position	0	1: The paper can be pulled out by weak force	2: The paper cannot be pulled out
D. Coordination/speed[f] (subtotal/6 points)		None	Sufficient	Insufficient
Tremor		0 : Noticeable	1 : mild	2 : None
Dysmetria		0: Noticeable	1 : mild	2 : None
Time		0 : >6 seconds	1 : 2–5 seconds	2 : <2 seconds
Total score			// 66 points	

[a]Lift the hand up to the ear on the paralyzed side in a sitting position
[b]Touch the knee on the non-paralyzed side in a sitting position
[c]This test should be performed only when a patient achieves a perfect score in IV
[d]Give assistance to keep the position of the shoulder and the arm if needed (Adopted from Ref. [11])
[e]Give assistance to keep the arm at 90 degrees if needed
[f]Repeat the movement of putting the index finger on the paralyzed side to the nose five times as fast as possible with eyes closed (Adopted from Ref. [11])

as the forearm's pronation and supination and the elbow joint's extension. Each item is rated on a three-point ordinal scale: 0 point (cannot), 1 point (can perform partially), and 2 points (can perform fully). This means that the maximum motor performance score for the upper limb that can be attained is 66 points.

WMFT is an objective evaluation method that was created to evaluate the function of the upper limb on the paralyzed side before and after CI therapy. It has come to be used more frequently, especially in Western countries. It consists of 15 tasks (6 physical exercises and 9 object manipulations), and the required time for completing each task is measured and recorded. Each task should be completed within 120 seconds. When the task was not completed within 120 seconds, the performance time of the task was recorded as 120 seconds. Eventually, the total performance time (seconds) of all 15 tasks or the natural logarithm of the average performance time are considered as an evaluated value. The smaller this value is, the better the upper limb function is. In addition, the quality of movement is determined on a six-level rating system in the functional ability scale (FAS), from 0 (cannot move at all) to 5 (can move almost normally).

ARAT is not very common in Japan. However, some reports indicate that it has high reliability and validity as an evaluation method of poststroke upper limb function [12, 13] and it is widely used in the United States and Europe. It was developed based on the upper extremity function test (UEFT) [14] by Lyle [15] to assess the poststroke upper limb function. UEFT was developed to monitor the upper limb functions related to daily life and consists of 33 evaluation items in total. In ARAT, the 4 major functions of upper limbs, that is, (1) grab, (2) grasp, (3) pinch, and (4) gross motor, were selected from the evaluation items of UEFT and organized into 19 items in total. ARAT's features are as follows: it is relatively simple and easy to use because the evaluation requires only a mean of 5 to 10 minutes, gross motor-related subtests are included in the items, and its score can be widely distributed even in cases of severe paralysis.

2) Evaluation of Use in Daily Life

We make an evaluation of the amount of use (AOU) which subjectively shows how often the upper limb on the paralyzed side is used in daily life as well as the quality of movement (QOM), which shows how well it is used. In fact, there are few scales to evaluate the severity of upper limb paralysis from the point of view of the ADL and instrumental activity of daily living (IADL). Therefore, evaluation is made by using (1) a Japanese version of MAL (Tables 2.8 and 2.9) prepared by Takahashi et al. [16] through summarizing a motor activity log (MAL) that has already been put to practical use and (2) a Jikei assessment scale for motor impairment in daily living (JASMID) (Tables 2.10 and 2.11) devised by Ishikawa et al. in our department [17].

MAL comprises 14 ADL items that were devised based on the Western lifestyle and has come to be used more frequently, mainly in the United States.

Table 2.8 Japanese version of motor activity log

Motion evaluation items	AOU	QOM
1. Read a book/newspaper/magazine while holding it		
2. Wipe my face and body with a towel		
3. Pick up a glass		
4. Brush my teeth with a toothbrush		
5. Put on makeup/shave		
6. Open a door by using a key		
7. Write a letter/type		
8. Stand still in a stable position		
9. Put my arm through the sleeve		
10. Move an object with my hand		
11. Eat by holding a fork or a spoon		
12. Comb hair by using a brush or a comb		
13. Hold a cup by grasping its handle		
14. Fasten the front buttons		
Total		
Mean (total/number of motion evaluation items which have been performed)		

Reprinted from Ref. [16]

Table 2.9 Evaluation scale for Japanese version of motor activity log

AOU (amount of use)
0. Do not use my weaker arm (not used; 0 % of pre-stroke)
1. Occasionally use my weaker arm, but only very rarely (very rarely used; 5 % of pre-stroke)
2. Sometimes use my weaker arm but do the activity most of the time only with my stronger arm (rarely used; 25 % of pre-stroke)
3. Use my weaker arm about half as often as before the stroke (50 % of pre-stroke).
4. Use my weaker arm almost as often as before the stroke (75 % of pre-stroke).
5. Use my weaker arm as often as before the stroke (100 % of pre-stroke)
QOM (quality of movement)
0. My weaker arm is not used at all (not used)
1. My weaker arm is moved during the activity but is not helpful (very poor)
2. My weaker arm is of some use during the activity but needs some help from the stronger arm, moves very slowly, or with difficulty (poor)
3. My weaker arm is used for the activity but the movements are slow or it is not strong enough (fair)
4. The movements made by my weaker arm for the activity are almost normal but not quite as fast or accurate as normal (almost normal)
5. The ability to use my weaker arm for the activity is as good as before the stroke (normal)

Adapted from Ref. [16]

Table 2.10 JASMID

Motion evaluation items[a]	AOU	QOM
1. Write with a pen[b]		
2. Eat with chopsticks (pick up side dishes)[b]		
3. Brush my teeth with a toothbrush[c]		
4. Clip the fingernails		
5. Open and hold an umbrella		
6. Put on makeup/shave[c]		
7. Wash my face		
8. Comb hair by using a brush or a comb		
9. Fasten the front buttons of a shirt[d]		
10. Turn a page of a newspaper/a magazine and read it[d]		
11. Open and close the lid of a plastic bottle[d]		
12. Cut toilet paper roll[d]		
13. Open a can of juice[d]		
14. Fasten a belt/put on a brassiere[d]		
15. Put on socks (for both feet)		
16. Wring out a rag or a towel		
17. Hang up a jacket on a hanger		
18. Take some coins out of a purse		
19. Tie shoelaces		
20. Wear a tie/necklace		
Engage in hobbies		
Engage in work/do housework		
Total		

Reprinted from Ref. [17]
[a]Regardless of the use of self-help tools such as an electric toothbrush and chopsticks with handles
[b]For motion evaluation items 1 and 2, motions as a "supporting hand" are excluded
[c]For motion evaluation items 3 and 6, preparing motions are not evaluated
[d]For motion evaluation items 9–14, motions as a "supporting hand" are also included

On the other hand, JASMID was examined and developed to solve the problems of adapting MAL directly to patients in Japan. It is a scale to evaluate the severity of upper limb paralysis from the point of view of ADL and IADL in line with the Japanese lifestyle. We are working toward practical use of JASMID.

C. Intensive OT in NEURO-15

1) Concept

NEURO-15's goal is for patients to acquire a habit of using the upper limb on the paralyzed side (as much as possible) also in daily life after discharge when they need.

Table 2.11 Evaluation scale and scoring system of JASMID

AOU (amount of use)
0. Do not use my weaker arm at all (do not want to use it)
1. Cannot use my weaker arm at all (want to use it but cannot)
2. Use my weaker arm a little (rarely use it)
3. Sometimes use my weaker arm (only 50 % of pre-stroke)
4. Often use my weaker arm (use it less frequently than pre-stroke)
5. Always use my weaker arm (use it as often as pre-stroke)
QOM (quality of movement)
0. Can rarely use my weaker arm (even if try to do it)
1. Find it very difficult to use my weaker arm (quite difficult compared to pre-stroke)
2. Find it moderately difficult to use my weaker arm (50 % of difficulty compared to pre-stroke)
3. Find it slightly difficult to use my weaker arm (slight difficulty compared to pre-stroke)
4. Do not find it difficult to use my weaker arm at all (almost the same as pre-stroke)
Scoring system
Frequency of use = sum of AOU/(number of motion items scored at 1 to $4 \times 5) \times 100$
Quality of movement = sum of QOM/(number of answered motion items $\times 5) \times 100$

Reprinted from Ref. [17]

Most patients who have received NEURO-15 said as follows: “I cannot imagine moving my weaker upper limb,” “I don’t know how to move it,” or “I’ve forgotten how to use it.” We attribute this to the fact that most patients have fallen into a motion pattern specific to chronic stroke hemiplegia (a situation where labored movements are repeated because of the central hypotonia and this causes muscle tone in the peripheral portion to increase, which inhibits isolated movements).

We therefore believe that it is necessary to assess the states of motor paralysis through a comprehensive evaluation, as follows: (1) it is functionally impossible for the patient to do it; (2) the patient has not learned how to use it, although he/she has a function that can be used; or (3) as a result of prioritizing work efficiency when using the nonparalyzed upper limb, the patient has learned not to use it (learned nonuse) and does not use it even if he/she can.

In any case, we have made interventions in consideration of the fact that most patients have fallen into a situation where there are less opportunities to use their fingers on the paralyzed side as a result that the paralyzed upper limb has rarely been used and the nonparalyzed upper limb has mainly been used in daily life over a long period of time.

2) Point of the Program Structure

In the NR, the major functional recovery process from the subacute to chronic phase is considered as a reorganization of the neural mechanism in a usage frequency-dependent manner. Therefore, it is considered that the volume of training, training time, training content, and environment, including task-oriented movements, are

important for performing the NR efficiently and effectively and that rebuilding the brain function can be promoted, especially by increasing the volume of task-oriented training [18, 19].

NEURO-15 has been implemented as a 15-day rehabilitation program, including about 4 hours intensive OT daily. This means that it includes sufficient training time, as described above. In addition, its short-term program aims to acquire a patient's needs after fully understanding his/her functional capacity. To achieve this goal, it consists of step-by-step programs that aim to acquire the movements that the patient needs most and that will probably be used more often in his/her daily life, such as those for ADL and hobbies. It is safe to say that this is task-oriented training.

If we conclude that it is very hard to get the patient to achieve his/her needs, the therapist may make a proposal to perform training including movements considered acquirable. In any case, it is important to carry out interventions that can improve the quality of life after discharge. And it is necessary to prepare a self-exercise program suitable for each patient based on the goal of continuing to use the upper limb on the paralyzed side.

D. Actual Practice of Intensive OT in NEURO-15

1) Questionnaire Before Admission

Our department conducts a survey using a questionnaire (by mail) prior to admission and makes an effort to understand the patient's requests and needs about the treatment and his/her use of the upper limb on the paralyzed side in daily life. By referring to the survey results, we provide an individual OT program with an emphasis on meeting the patient's needs.

2) One-to-One OT

Considering the clinical presentations of the study patients in NEURO-15 described so far, if an occupational therapist asks a patient to move only the distal portion without fully considering the motor disorder of the central portion, the stability and individuality of movements were ignored, resulting in gross motor movement without dexterity and simply causing patients to "overstrain" themselves. In other words, if a patient trains the upper limb on the paralyzed side in his/her own way, there is a risk that it would end up learning the incorrect movements with the result that a desirable recovery would not be achieved. For this reason, it is especially important to conduct iterative training with facilitation procedures and provide practical ADL and IADL training with direct intervention of an occupational therapist.

We basically start our individual OT in a hands-on manner and provide a patient with "infallible learning" and make an intervention for efficient motor learning.

Then, while observing the patient's motion patterns and his/her status of motion acquisition, we gradually try to shift to a hands-off manner. In addition, considering the importance of the movement of both hands in ADL, we maintain a basic attitude of conducting training without suppressing the movements of the upper limb on the nonparalyzed side. We specifically focus on the following nine points:

(i) Daily routine movements should be adequately included in the training tasks.
(ii) All factors of gross motor, dexterity, and combined movements (by both hands) should be included in the training tasks.
(iii) The upper limb portion to be focused on during training should be clearly shown.
(iv) The functional training should be conducted in a step-by-step manner toward the acquisition of movements and activities.
(v) A lot of movements which the patient can continue in self-exercise at home or in the ADL after discharge should be included in the training.
(vi) In principle, the upper limb on the nonparalyzed side should not be restrained.
(vii) Feedback about the movements should be delivered not only by verbal instructions but also by manual intervention.
(viii) The patient's images of the movements and activities should be enhanced by describing the training contents in detail every time and obtaining his/her understanding, Immediately after admission to the hospital, gross motor exercise accounts for the majority of the training, approximately 80 %. The training program should be structured so that the dexterity motion and combined motion exercise will increase over time and finally account for the majority of the program.
(ix) The patient's active attitude and our assistance in his/her training and learning should be emphasized during the training. It is important to show our support for the patient by giving positive feedback.

a. Training Structure

Our training structure can be roughly classified into (i) gross motor movement, (ii) functional training including dexterity motions, and (iii) applied training including combined motions. During hospitalization, the proportions of these three types of training are gradually changed depending on the stage, as shown in Fig. 2.3.

Patients with poststroke hemiparesis have specific motion patterns such as hypotonic in the central portion (proximal muscle), unnatural hypertonic in the peripheral portion (distal muscle), and labored motions especially when starting up. Given these facts, patients should start mainly with gross motor training focusing on facilitations to improve the bearing properties of the central portion and to reduce hypertension in the peripheral portion. Subsequently, we try to gradually increase the percentage of facilitation training of the distal portions while improving the bearing properties of the central portion.

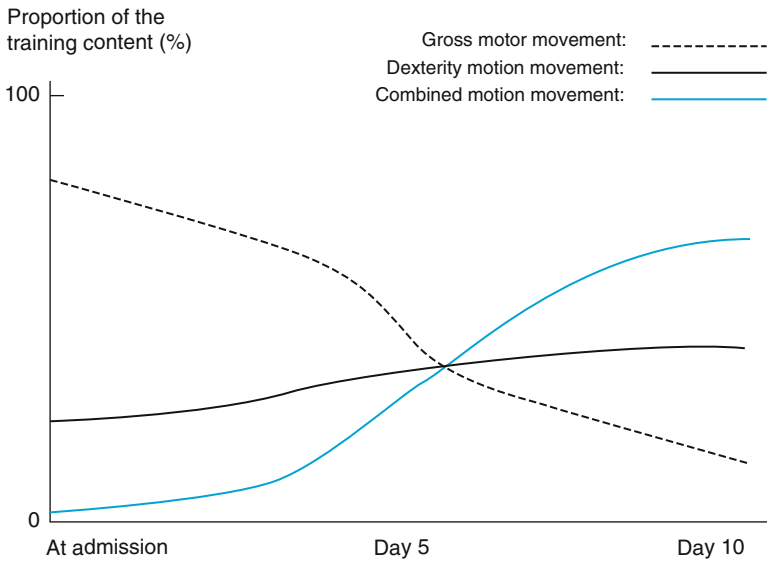

Fig. 2.3 Changes in weighting of the training content in NEURO-15
Immediately after admission to the hospital, gross motor exercise accounts for the majority of the training, approximately 80 %. The training program should be structured so that the dexterity motion and combined motion exercise will increase over time and finally account for the majority of the program

In practice, we make an intervention to improve the bearing properties and endurance of the body trunk and the center of the upper limb so that the function of the central portion, which is considered important in reaching movements, can be improved. In dexterity motion training, we conduct exercises such as facilitation to move the distal portion individually, as well as an object manipulation exercise to improve grasping and manipulating movements.

b. Points of the Combined Motion Training (by Both Hands)

In combined motion training, we conduct motion training directly linked to the actual ADL, focusing on bimanual actions based on the patient's needs in a step-by-step manner. ADL movements in particular require coordinated motions of both hands. As described above, however, many patients receive different sensory information from the upper limb on the paralyzed side compared to before their stroke and show poor bimanual movements and activities by learned nonuse.

Therefore, in the one-to-one OT, we provide guidance and intervention to reacquire the coordination of both hands such as in eating and grooming. In life during hospitalization as well, we instruct patients to actively use the upper limb on the paralyzed side and to repeatedly learn how to do motions and activities. In com-

bined motion training, we consider to use self-help equipment in some cases and develop ideas to achieve the patient's needs and goals as much as possible.

Combined motion training is introduced around the midterm of hospitalization. However, in some cases, such as patients who are good at isolated movement and simply have a problem of learned nonuse, we proactively introduce bimanual motion training and ADL and IADL training from the start-up period and make a flexible intervention according to the severity of motor paresis and usage of the paralyzed side.

In this way, patients undertake functional training and relearn how to move in NEURO-15. They tend to get a "good response" compared to before admission, with comments such as "Now I can move more easily," "My movements are getting smoother," and "There are more things I can do." As a result, the patient's mind and attitude about the upper limb on the paralyzed side changes, and he/she starts thinking that he/she "tries to" or "wants to" use it in the ADL. We believe that habitual repetitive practice can help improve the frequency of use of the upper limb on the paralyzed side and effectively eliminate the learned nonuse.

3) Self-Exercise Program

An inpatient does a self-exercise program by himself/herself based on the prepared handouts that indicate the points of the self-exercise and cautions to review the training in one-to-one OT. If a problem occurs in the self-exercise, it should be reviewed in the next one-to-one OT with help from the therapist in charge. We create a self-exercise program after discharge including important points about the acquired movements in the self-exercise during hospitalization. Our handouts show ADL settings where the patient can use the upper limb on the paralyzed side. Thus, we have developed ideas to give the patient a specific image of using the upper limb on the paralyzed side in ADL. In addition, we provide an explanation about improved functions, acquired movements, and how to do the self-exercise also to supportive family members at the time of discharge, which can help them understand the current status of the patient's dysfunction and recovery.

4) Actual Training Program

a. Gross Motor Training

Movement patterns specific to chronic stroke patients include central hypotonia and peripheral unnatural hypertonia. Therefore, at the start of one-to-one OT, we make an intervention focusing on the gross motor training shown in Fig. 2.4 in order to improve voluntary properties, bearing properties, and endurance of the central portion and to reduce tension in the peripheral portion.

Fig. 2.4 Gross motor training

b. Dexterity Motion Training

Dexterity motion training is introduced at the same time as the gross motor training, and we make an intervention to gradually increase the percentage of facilitation training in the peripheral portion. Typical types of training are shown in Fig. 2.5.

c. Combined Motion Training

Combined motion training including bimanual behaviors, such as object manipulation training and ADL, is applied when the patient has already acquired the voluntary wrist's movement to some extent, when the patient can gradually move the wrist joint individually, or around the midterm of the training intervention. Typical training types are shown in Fig. 2.6.

3 Treatment Results of the Multicenter Trial: Introduction of Multicenter Data

In April 2008, our group started NEURO, which is a combination treatment of low-frequency rTMS and the intensive OT for poststroke patients with upper limb hemiparesis. As mentioned above, after confirming its efficacy and safety in a few cases, we have extensively conducted its 15-day protocol called NEURO-15 since April 2009.

Fig. 2.5 Dexterity movement training

Fig. 2.6 Combined motion training

The protocol is now being conducted in the 11 institutions shown in Fig. 2.7. As of October 31, 2014, the protocol had been applied to a total of 2008 patients in 13 institutions (2 institutions are not currently providing the protocol for some reason). In this section, however, we show the data as of August 31, 2012, when the protocol had been applied to a total of 1008 patients. This data was published in *Japanese*

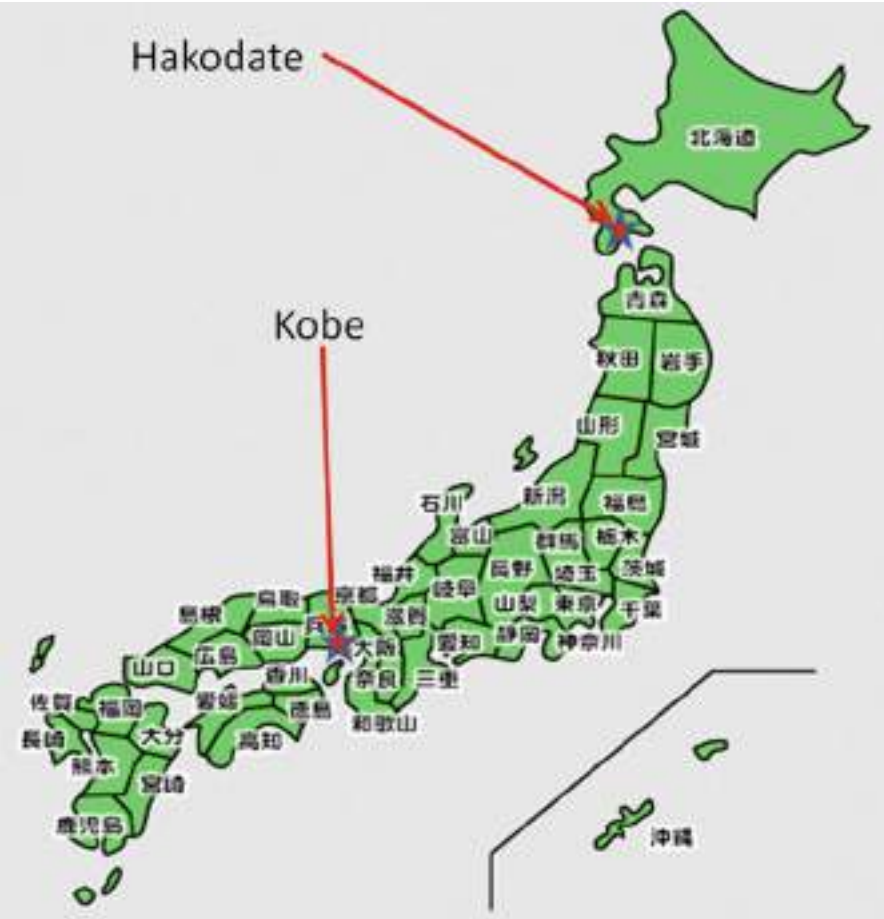

Fig. 2.7 List of the institutions conducting NEURO-15 (As of November 1, 2014)

Journal of Stroke in 2013 [20]. At that time, the protocol was being conducted in eight institutions.

The eight institutions include the following:

The Jikei University Hospital (Minato-Ku, Tokyo)
The Jikei University Daisan Hospital (Komae, Tokyo)
Shimizu Hospital, The Kyosaikai Medical Foundation (Kurayoshi, Tottori)
Tokyo General Hospital, The Kenkoukai Medical Foundation (Nakano, Tokyo)
Nishi-Hiroshima Rehabilitation Hospital, The Houwakai Medical Corporation (Hiroshima, Hiroshima)
Kimura Hospital, The Jujinkai Medical Corporation (Sabae, Fukui)
Aizawa Hospital, The Jisenkai Social Welfare Juridical Person (Matsumoto, Nagano)

Suwa no Mori Hospital, The Koshinkai Medical Corporation (Oita, Oita)
For some reasons, Aizawa Hospital and Suwa no Mori Hospital ended the provision of the protocol before November, 2014.

A. Overview of the Study Patients

The report on this multicenter study includes 1008 patients who visited 1 of the 8 institutions during the period of April 1, 2009, to August 31, 2012, and wanted to participate in NEURO-15 and met all the eligibility criteria described above.

The clinical backgrounds of the study patients are shown in Table 2.12 [20]. The mean age at admission was 61.1 ± 12.4 years, and the mean elapsed time from stroke onset to treatment was 81.5 ± 88.5 months. With regard to the subtypes of stroke, 522 patients with intracerebral hemorrhage and 486 patients with cerebral infarction were included. While 570 patients had dominant upper limb hemiparesis, 438 patients had nondominant upper limb hemiparesis.

B. Training Contents

The training content of NEURO-15 was as follows:

(i) Low-frequency rTMS was performed for the patient in sitting position using MagPro R30 and a figure-8 coil.
(ii) Stimulation was performed on the site where the largest MEP in the FDI muscle of the upper limb on the nonparalyzed side can be elicited within the primary motor area of the nonlesional hemisphere.
(iii) The intensity was set at 90 % of the motor threshold of the muscle (the minimum stimulus intensity that can produce MEP at the stimulation site).

Table 2.12 Clinical characteristics of patients treated with NEURO-15

Age at the intervention, years [range]		61.1 ± 12.4 [18–90]
Gender	Female	337 (33 %)
	Male	671 (67 %)
Time after stroke onset, months		81.5 ± 88.5 [12–338]
Subtype of stroke	Intracerebral hemorrhage	522 (52 %)
	Cerebral infarction	486 (48 %)
Side of upper limb hemiparesis	Dominant hand	570 (57 %)
	Non-dominant hand	438 (43 %)
Brunnstrom Recovery Stage for hand-fingers	Stage 3	202 (20 %)
	Stage 4	360 (36 %)
	Stage 4	446 (44 %)

Adopted from Ref. [20]

(iv) rTMS was immediately discontinued when an adverse event or adverse reaction occurred.
(v) The protocol during hospitalization consisted of low-frequency rTMS and an intensive OT. One session of low-frequency rTMS of 1 Hz lasted 20 minutes (a total of 1200 pulses).
(vi) 120-minute intensive OT as a combination therapy consisted of 60-minute one-to-one OT and 60-minute self-exercise. Two sessions were performed every day except the day of admission, the day of discharge, and Sundays.
(vii) Upper limb motor function was evaluated by using FMA items related upper limb and WMFT log performance time.
(viii) Upper limb function was evaluated at admission, at discharge, and at 4 weeks after discharge.

C. Training Results

First, we describe the safety of the protocol. All 204 patients completed NEURO-15, and no one showed a change in vital signs, such as blood pressure and pulse. Exacerbation of neurological findings and deterioration of motor function were not observed in any patient. Of the 1008 patients who completed this protocol, 271 patients were evaluated at 4 weeks after discharge. Of these 271 patients, none showed any adverse reactions during the 4 weeks after discharge.

Viewing the evaluations of 204 patients at admission and discharge, FMA showed a significant improvement from 45.3 ± 12.1 points to 49.7 ± 10.4 points (Fig. 2.8) [20], while WMFT log performance time also improved significantly from 2.78 ± 1.07 to 2.43 ± 1.22 (Fig. 2.9) [20].

The FMA score of the 271 patients who were evaluated at 4 weeks after discharge was 46.7 ± 10.5 points, 50.6 ± 8.7 points, and 49.9 ± 9.3 points at admission, at discharge, and at 4 weeks after discharge, respectively. These results indicate that both the scores at discharge and at 4 weeks after discharge showed a significant improvement compared to that at admission (Fig. 2.10) [20].

WMFT log performance time shifted from 2.46 ± 1.30, 2.11 ± 1.29, to 2.18 ± 1.37. It also showed a significant improvement at discharge and at 4 weeks after discharge compared to that at admission (Fig. 2.11) [20].

Both the log performance time of FMA and WMFT showed a significant improvement at 4 weeks after discharge as well, which indicates that the improvement of the motor function can be maintained even at 4 weeks after receiving NEURO-15.

The multicenter study described above demonstrated that the current protocol of NEURO-15 is safe and highly effective as well as generally feasible in many institutions.

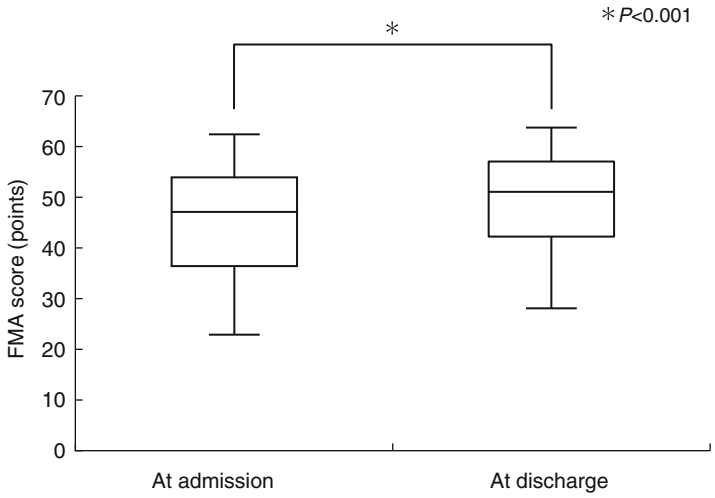

Fig. 2.8 Change in FMA score in patients receiving NEURO-15. FMA score at discharge showed a significant improvement compared to that at admission [20]

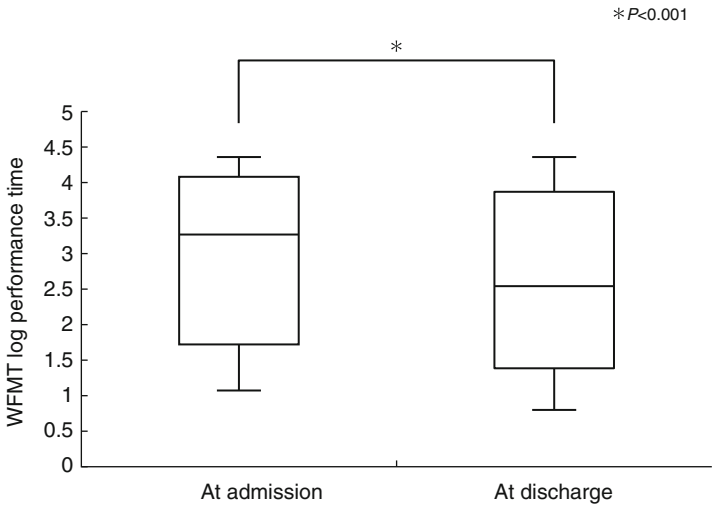

Fig. 2.9 Change in WFMT log performance time in patients receiving NEURO-15. WFMT log performance time showed a significant improvement compared to that at admission [20]

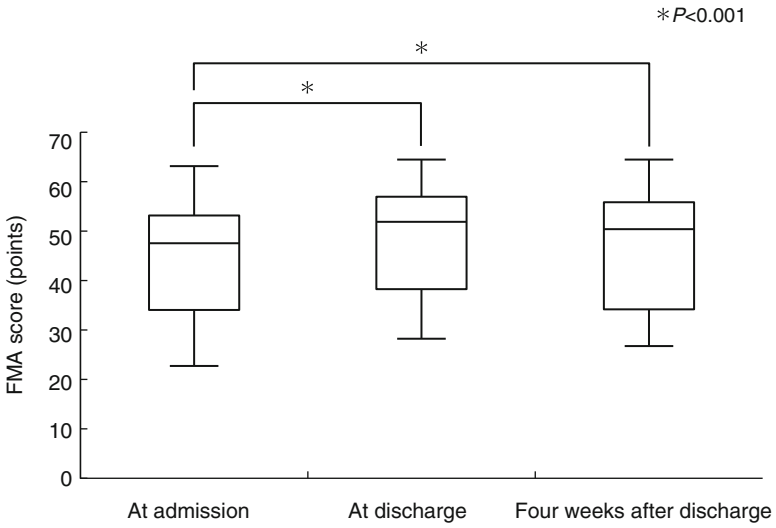

Fig. 2.10 Evaluation at four weeks after discharge and change in FMA score in evaluated patients. FMA score at discharge and at four weeks after discharge showed a significant improvement compared to that at admission [20]

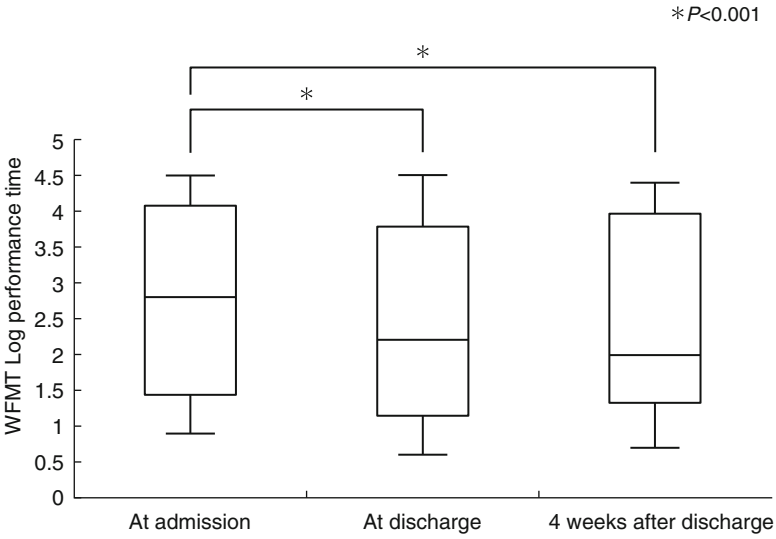

Fig. 2.11 Evaluation at four weeks after discharge and change in WFMT log performance time in evaluated patients. WFMT log performance time at discharge and at four weeks after discharge showed a significant improvement compared to that at admission [20]

4 Efforts by Each Institution for Improving the Quality of rTMS Treatment

As described above, the safety and efficacy of NEURO-15 has been demonstrated with the results of the previous studies. From past experience, we consider that OT is essential in NEURO-15 and there is a possibility that OT may contribute to improving poststroke upper limb hemiparesis by producing synergies with rTMS, which eliminates the imbalance of interhemispheric inhibition. While NEURO-15 is currently being conducted at 11 institutions, each institution is still learning through trial and error and seeking more effective interventions through consideration and generating unique ideas. Efforts by each institution are described as follows.

A. Combined Therapy with PT

In rTMS in NEURO-15, stimulation is performed to the primary motor area of the nonlesional hemisphere, where the largest MEP in the FDI muscle of the unaffected upper limb can be elicited.

In Penfield's homunculus (p. 104), the area responsible for the lower limb function is located near the fissura interhemisphaerica at considerable depth. Thinking anatomically, it is difficult to have a positive effect on the lower limb motor function through magnetic stimulation with a figure-8 used in NEURO-15. However, 20–30 % of patients who received stimulation to the upper limb motor area actually felt an effect on lower limb motor function. This suggests the possibility that if the plasticity around the cerebral lesions responsible for upper limb functions has increased after stroke onset, not only the area near the fissura interhemisphaerica but also the area responsible for lower limb function can be recovered.

In addition, most patients who are hospitalized to receive NEURO-15 hope to improve their walking ability as well as upper limb motor function, and many ask us to perform combination therapy with physical therapy (PT). In general, many patients with stroke undertake self-exercise after discharge from a recovery phase rehabilitation hospital and continue rehabilitation with the use of long-term care. However, some patients are hospitalized to receive NEURO-15 1 year or more after stroke onset without receiving sufficient training or even without using an adequate brace.

Therefore, some institutions employ combination rehabilitation with PT to improve the lower limb motor function and walking function. In exercise therapy for improving the lower limb motor function, we make a therapeutic intervention with emphasis on facilitation exercise and stretch exercise of the muscle spasticity based on the degree of recovery of the lower limb on the paralyzed side as well as

trunk muscle training through basic movements such as getting up and standing up. We also perform applied gait training, including balance training in a standing position and stair-climbing, to improve practical lower limb ability.

According to a recent report, a significant improvement in both walking and balance ability was observed in patients receiving CI therapy after performing combined treatment with PT focusing on walking compared to the preintervention period [21]. Intensive rehabilitation during hospitalization similar to CI therapy is also being performed in our ongoing NEURO-15. We believe that this is useful and highly satisfactory for patients who can "re-learn" by therapeutic rehabilitative intervention.

B. Training Using Photos or Videos

As needed, many institutions give patients feedback using photos and videos. Mancebo et al. [22] and van Vliet et al. [23] reported that visual feedback using photos and videos is useful in rehabilitation for poststroke upper limb hemiparesis unless the patient has visual impairment, unilateral spatial neglect, or severe impaired attention. We consider that these kinds of visual feedback help patients understand a specific posture and motion images and can also improve the patient's motivation during the training period.

Many institutions utilize these types of training in self-exercise and guidance after discharge, described below. They take photos of activities in daily life which the patient could successfully achieve during hospitalization and prepare unique manuals along with easy-to-understand advice. At discharge, these institutions give the patient these materials along with a self-exercise program and provide guidance to keep using the upper limb on the paralyzed side at home.

C. Devices About Self-Exercise Program

Each institution has come up with its own approach to self-exercise program. The main goal of self-exercise is to improve muscle strength and endurance, to perform motion repetition training, and to conduct task-oriented training to improve ADL. In this context, many institutions prepare achievable self-exercise programs tailored to the individual patient, which consist of not only basic training programs but also applied training related to cooking procedures and the patient's hobbies which were known through an interview at admission (Tables 2.13 and 2.14). These institutions conduct an occasional review of the self-exercise programs and intensity according to the patient's level of achievement and give feedback. The concept of a transfer package described below is also incorporated and utilized when creating self-exercise program.

Table 2.13 An example of a self-exercise program (1)[a]

Self-exercise program for Mr./Ms. XX XX
1. Ball lifting (20 times × 2 sets)
2. Wall wiping (up-and-down, 20 times × 2 sets) *If there is pain, please do this exercise moderately *Keep the right arm close to the body with the left hand on the wall to support yourself
3. Small pegs (peg and unpeg/invert) *Do this exercise while holding the peg with the ring and little fingers
4. Marble rolling (10 times per set) *Use large marbles *Roll them inside the palm of your hand
5. Applied training 1. Use chopsticks well 2. Write words well

[a]Take a rest when you feel tired

Table 2.14 An example of self- exercise program (2)[a]

Self-exercise program for Mr./Ms. XX XX
1. Lift a ball above your head with both hands (15 times × 2 sets)
2. Lift a ball at a right angle with both hands (15 times × 2 sets)
3. Spin a ball with both hands (15 times × 2 sets)
4. Do push-ups on a table (15 times)
5. Do push-ups against a wall
6. Stretch the medial rotator (maintain 10 seconds × 10 times)
7. Move thick pegs
8. Writing exercise

[a]Take a rest when you feel tired

Do not use my weaker arm at all (do not want to use it)

D. Evaluation and Direction After Discharge

Nakama [24] mentioned that self-exercise at home is not just voluntary training but behavioral modification from the patient and his/her family's dependent and passive activities to their proactive and positive activities. At the time of discharge from hospitalization for NEURO-15, the therapist explains the achievements and results during hospitalization and provides direction about self-exercise after discharge. Important points in self-exercise are first, to have the patient acquire the habit of "keeping on using the upper limb on the paralyzed side" in daily life after discharge; second, to maintain the acquired function, continue to provide guidance by assessing whether the patient is training correctly and making modifications when necessary; and finally, share the information not only with the patient and medical professionals but also with the patient's family.

Table 2.15 Directions of self-exercise

Evaluation	Body functions, activities, social environment, personality, and needs
Problem analysis	Share the problem and analyze what movements the patient needs. Make clear the purpose of the exercise
Goal setting	Set an achievable, sustainable and reasonable goal. Set a goal that offers an image of future life and a goal that should be achieved in the immediate future in accordance with the patient and his/her family's chief complaints and requests, as well as a prognosis based on an objective evaluation and problem analysis from the perspective of each medical profession
Exercise content setting	Exercise can include a movement that fits to the patient's body function, repetitive practice of living activities, or social participation itself. Create a specific exercise content
Monitoring	Check the patient's status when he/she visits the hospital or by phone. Ask him/her to shoot a video of his/her daily life and give feedback by reviewing it

Reference [24]

Nakama also said in the guidance for self-exercise after discharge that evaluation, problem analysis, goal setting, exercise content setting, and monitoring are important in intervention in self-exercise after discharge (Table 2.15) [24].

Based on these facts, each institution has tried to develop a variety of ideas. Many institutions encourage their patients to use movements acquired during hospitalization even in daily life after discharge and set a specific and achievable goal. Then, step-by-step exercises according to individual ability are shown in detail using illustrations and photos. In addition, as described above, patients are provided with training advice and photos taken during hospitalization which show the movements they successfully did or they became able to do through the exercise (Figs. 2.12 and 2.13).

One institution uses a mountain climbing analogy to encourage patients to understand the current status of the upper limb on the paralyzed side and what is needed in future exercise (Fig. 2.14). They also ask patients to record what has changed in daily life and try to support their behavior modification (Fig. 2.15). They use this record to understand the patient's situation in daily life after discharge and to provide guidance after discharge. Some institutions have onsite facilities for visiting rehabilitation or ambulatory rehabilitation, which enables them to provide continuous guidance even after discharge.

At the time of discharge, these institutions also provide an explanation and guidance about achievable movements to the family members to share information. Some institutions ask not only the patient but his/her family to check how the patient uses the upper limb on the paralyzed side at home and whether he/she is able to continue the exercise. In addition, they conduct an interview at four weeks after discharge to track activities of daily living and the exercise, which is reflected in the evaluation and future exercises, and again, some advice is provided by the medical staff.

Fig. 2.12 An example of a booklet for guidance at the time of discharge (Jikei University Hospital)

Fig. 2.13 An example of a booklet prepared for guidance at discharge (Kimura Hospital)

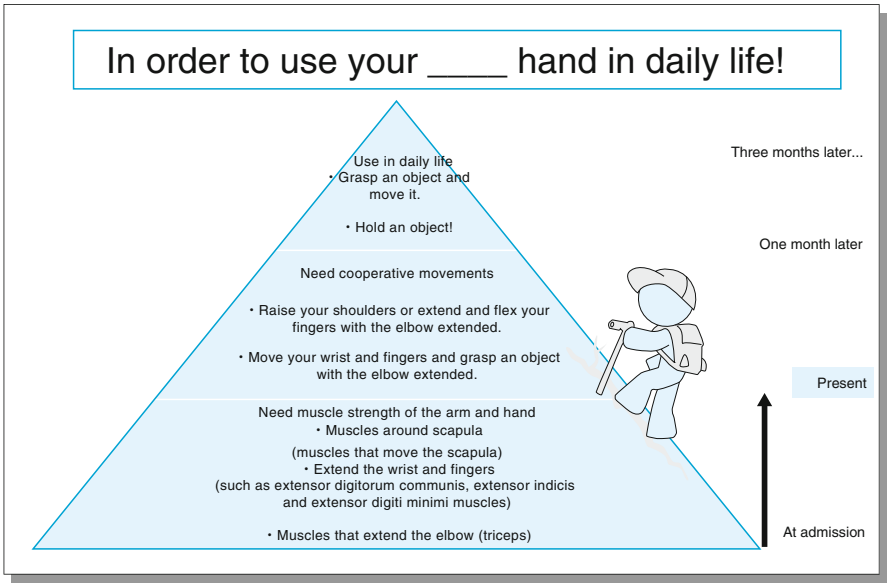

Fig. 2.14 Guidance to modify behaviors at and after discharge. This institution gives an explanation using easy-to-understand illustrations so that the patient can understand the status of his/her paresis at discharge and make an effort to improve the motivation and modify behaviors (Data provided by Aizawa Hospital)

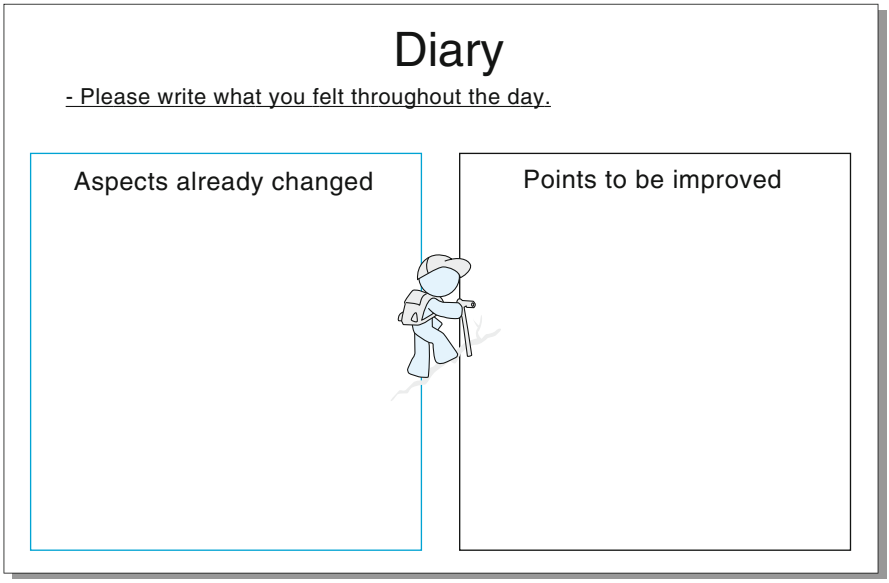

Fig. 2.15 Record-keeping form for patients to facilitate behavior modification after discharge (Data provided by Aizawa Hospital)

E. Initiatives During Hospital Ward Life

As a rule, a hospitalization for NERUO-15 lasts 15 days. To efficiently promote behavioral modification and improvement of the upper limb on the paralyzed side during this short period, nurses at some institutions check how patients use the upper limb on the paralyzed side during their stay in the hospital ward. It is important that nurses understand the patient's use of the upper limb on the paralyzed side, something that might be difficult for physicians and therapists, and identify the patient's problems and concerns about the use of the upper limb on the paralyzed side through communication with the patient. One institution uses its own checklist shown in Fig. 2.16 and encourages patients to use the upper limb on the paralyzed side during their time in the hospital ward, including use in the early morning and at night.

F. Application of the Transfer Package

The transfer package is a strategy of efficient occupational therapy in CIMT proposed by Taub et al. [25] and Morris et al. [26] in 2006. It is a behavioral strategy to increase the frequency of use of the hand on the paralyzed side and improve the quality of movement in the ADL in real life. Many patients have not only a dysfunction caused by post-stroke upper limb hemiparesis but also a behavioral disorder due to the nonuse of the upper limb on the paralyzed side. Therefore, with the transfer package shown in Table 2.16, the therapist and the patient plan a behavioral strategy to improve the upper limb on the paralyzed side during hospitalization and conduct training to overcome barriers and to sustain its effect even after discharge. A major difference between the transfer package and the traditional training is that in the latter, a patient is passively provided with his/her exercise contents and training methods by a therapist and that in the former patient and therapist cooperate to create training methods and steps to achieve the next goal. This will be described in detail along with the contents of Table 2.16.

(i) In monitoring, use the MAL at the time of admission as a subjective evaluation measure to understand the status of the ADL and assess how the patient uses the upper limb on the paralyzed side in self-exercise and in ADL and how the training is proceeding.
(ii) In problem solving, pick out hard-to-do movements in daily life and during hospitalization, consider why they are hard to do, and have the patient work on a solution to make them possible.
(iii) In behavioral contract, clarify the role of the upper limb on the paralyzed side in daily life and during hospitalization, and make it clear (promise) that the patient should work on the selected solution and use the upper limb on the paralyzed side in daily life.

Rating scale of the use of the paralyzed side in daily life

Name ( ) Age (years old) Male / Female Dominant hand (right / left) Paralyzed side (right / left)

Rating 0: cannot do 1: can do 2: can do with a self-help tool or environmental adjustment 3: always do

Evaluated movement		Day 3	Day 5	Day 7	Day 9	Day 11	Day 13
		Mon	Wed	Fri	Sun	Tue	Thu
Eating	Can eat with both hands.						
	Can use chopsticks or a spoon with the hand on the paralyzed side.						
	Can hold a plate or keep it from moving with the hand on the paralyzed side.						
Grooming	Can wash your hands with both hands.						
Dressing	Can put on a shirt and take it off using both hands.						
Daily activities	Can take out a piece of tissue paper with the hand on the paralyzed side.						
	Can take a bill out of your wallet with the hand on the paralyzed side.						
	Can take a coin out of your purse with the hand on the paralyzed side.						
Physical status	Can move the thumb on the paralyzed side and touch all the other fingertips in order from the index finger. (1: index finger, 2: middle finger, 3: ring finger, 4: little finger)						
	Can raise the hand on the paralyzed side. (0: 45° or less, 1: 90°, 2: 135°, 3: 180°)						
Targeted movement							
Others							
Catch up test (Put an object on the table)							
Ball							
Pencil (Put it in parallel with your body)							
Paper (Can grasp the top of creaseless paper)							
Total score							

[Data provided by Suwa No Mori Hospital]

Fig. 2.16 Checklist of use of the upper limb on the paralyzed side in the hospital ward (Data provided by Suwa No Mori Hospital)

Table 2.16 What is the transfer package?

1. Monitoring	Monitoring of the training status and the use of the upper limb on the paralyzed side
2. Problem solving	Strategic planning of how to solve the problem in practice
3. Behavioral contract	Promise to work on solving the problem and to use the upper limb on the paralyzed side in daily life
4. Home skill assignment	List of activities conducted regularly
5. Home practice	Self-exercise at home
6. Daily schedule	Record of daily activities

(iv) In home skill assignment, gather information about the status of movements in daily life through an interview, evaluate the patient's needs and the result of the MAL, and reflect the feedback in the exercise.
(v) After that, conduct self-exercise (home practice) every day in addition to the training provided by the therapist, and continue updating suitable self-exercises for the individual patient on a daily basis.
(vi) As a daily schedule, record the activities and training details in daily life, have the patient understand the contents and review them, and make it possible to provide feedback about the qualitative changes of the upper limb on the paralyzed side.

Currently, some institutions are attempting to introduce this transfer package. A difference between the transfer package and the traditional exercises in NEURO-15 is that a patient is not passively provided with training and self-exercise plans created by a therapist, but rather the patient sets goals to promote behavioral modifications and voluntarily works on the exercises. However, the introduction of this transfer package in NEURO-15 has some problems: first, the status of the upper limb on the paralyzed side and the background of life differ from one patient to another; second, not all patients can always act on their own initiative. We think that there is room for further consideration.

G. Introduction of COPM

Each institution has developed its own ideas as described above. Under these circumstances, it is important to enable the patient to receive the maximum effect within a short period of time and to direct him/her to keep on doing the exercise after discharge. When the evaluation is made at the time of admission, it is sometimes difficult to set goals because some patients do not clearly understand the status of the upper limb on the paralyzed side and their own needs in ADL. In other words, there are occasionally cases that cannot be addressed by bottom-up rehabilitation. Therefore, one institution has attempted to introduce the Canadian occupational performance measure (COPM) to solve this problem.

COPM is an individual measure developed by Law et al. [27] and was created to evaluate a patient's perception over time when performing an occupation. In the occupational performance model in COPM, it is considered that an occupation is performed as a result of the interaction between a person, an occupation, and the environment. The occupations comprise three categories, namely, self-care, productive activities, and leisure: self-care means occupations by which patients keep themselves in good condition in daily life; productive activities include economic activities, daily housework, and school activities; leisure includes recreation other than their jobs or responsibilities.

We believe that a balance among these three categories is essential to perform an occupation and how well a therapist brings out the patient's skills as a performance element is important. This means that it is a top-down method provided at the first visit to bring out the performance element and utilize it in the exercise. A patient who is considered at the first visit to be unable to obtain a sufficient effect from the bottom-up method only requires intensive rehabilitation, including the top-down method. We think this should be reviewed in future studies.

5 Effect of rTMS on Spasticity

Through rehabilitation for patients with stroke in daily clinical practice, we have realized that many patients have spasticity along with hemiplegia.

Spasticity is observed in various ways. In some cases, it occurs when moving and inhibits the movement. In contrast, other patients conduct movement by using the spasticity. In the recovery process of poststroke patients with hemiparesis, muscle tonus and increased reflex are necessary to some extent. If spasticity occurs, however, the patient suffers from an awkwardness of movement and a pain as well as an impairment of ADL and the quality of life (QOL) [28]. Although we try to develop rehabilitation to enable patients to actively control muscle tonus, it is actually very difficult to achieve.

In recent years, an increasing number of studies have reported that better therapeutic effects have been obtained by performing rehabilitation after using medication or physical devices to reduce the excessively increased spasticity. The clinical application of rTMS by our group seems to be one of these studies [29]. In this section, we will describe the pathophysiology and the evaluation method of spasticity as well as the effect of rTMS on spasticity.

A. Pathophysiology of Spasticity

According to reports from Western countries, the frequency of spasticity occurrence in stroke patients increases with the time course of the disease: the incidence at 3 months and at 12 months after stroke is approximately 19 % and 38 %, respectively [30, 31].

The most well-known definition of spasticity proposed by Lance [32] in 1980 is that "Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome."

The diseases that cause upper motor neuron disorders include cerebrovascular disorder, cerebral palsy, head trauma, spinal cord injury, and multiple sclerosis. The neurological symptoms are classified into positive and negative symptoms. The positive symptoms include spasticity (findings such as increased muscle tone, exaggerated tendon jerks, stretch reflexes that affect other muscles and clonus) as well as focal dystonia, pathological synergy, pathological cocontraction, and increased flexor reflex such as Babinski reflex. The negative symptoms include a decrease in muscle output, muscle weakness including bradykinesia, motor paralysis, impaired isolated movement, dexterity impairment, easy fatigability, and impaired selective activities of the individual muscle.

Upper motor neurons act as neuronal pathways from the motor area of the cerebral cortex to neuronal cell bodies located in the anterior horn of the spinal cord at various levels. When part of them develop impairment such as mechanical damage, vascular insufficiency, and degeneration, an inhibitory signal to the reflex center located in the lower part of the brainstem and the spinal cord is reduced and is freed from control. It is thought that the excessive muscle tone and the increased spinal reflexes occur and the excitability of the spinal motor cells increase, which cause spasticity.

However, there is an opinion that spasticity does not occur when the pyramidal tract (including medullary pyramidal tract and lateral corticospinal tract), which is a projection path from the primary motor cortex corresponding to the Brodmann's area 4 to the spinal cord, is selectively damaged, while it occurs when the pyramidal tract is damaged along with Brodmann's area 6 [33]. There is also another opinion that spasticity occurs by dysregulation of reticulospinal and vestibulospinal tract which are inhibitory descending tracts [34].

The alpha motor neurons that control extrafusal muscle fibers and the gamma motor neurons that control intrafusal muscle fibers are involved in the occurrence of spasticity. Spasticity is characterized by a pathological enhancement of phasic stretch reflexes, which is one of the skeletal muscle reflexes at the spinal level. The muscle spindle is stimulated when the muscle is passively stretched. This stimulus is transmitted to the spinal cord through group Ia neural fibers, which stimulates the alpha motor neurons of the muscle and causes the stretched muscle to contract reflexively (stretch reflex). Group Ia neural fibers also have inhibitory synaptic connections with alpha motor neurons which control the antagonist and cause its relaxation (reciprocal inhibition).

For this reason, it is considered that the upper motor neuron disorders cause increased muscle spindle sensitivity, reduced presynaptic inhibition at the terminal of group Ia fibers, sprouting and formation of group Ia fibers, increased sensitivity of postsynaptic membrane, increased excitatory input, or reduced inhibitory input to

alpha motor neurons, which results in enhanced stretch reflexes and the impairment of reciprocal inhibition [35].

On the other hand, when gamma motor neurons are stimulated by impulses from the upper central nervous system, the intrafusal muscle fibers contract, and the activity of group Ia neural fibers are increased. This increase is transmitted to alpha motor neurons via the dorsal root, which promotes the stimulation. Such a pathway is called a gamma loop, and this reaction is also a mechanism that brings an increase in muscle tone. The descending tract from the upper central nervous system can indirectly control the activity of group Ia neural fibers in order to regulate the activity of gamma motor neurons. This means that the sustained activity of alpha motor neurons can also be controlled by the descending tract. When the activity of gamma motor neurons is increased, the muscle becomes more rigid and shows resistance to bending and stretching exercises. This is the increased muscle tone.

The combination of increased stretch reflexes and increased muscle tone caused through this process is considered spasticity. While the detailed pathophysiology of spasticity is still unclear, there is no objection that spasticity appears when descending information signals from the upper central nervous system to the spinal neural circuit become affected.

B. Evaluation of Spasticity

MAS and modified Tardieu scale (MTS) are the typical evaluation indices of spasticity. In particular, there have been many reports using MAS in Japan and overseas due to its simplicity.

MAS is an evaluation measure proposed by Bohannon et al. [36], who modified the Ashworth scale developed by Ashworth in 1964 and improved its accuracy. A patient's feeling of resistance when a joint is passively moved over the maximum ROM of each joint for 1 second (how much resistance he/she felt at what point in time) is recorded and evaluated. However, there are conflicting reports on MAS for poststroke patients with hemiparesis: some show that MAS has the interrater reliability, while others take the opposing view. When a detailed examination is required, the combined use with electrophysiological test is preferable. Typical examples of the electrophysiological test for spasticity include F-wave and H-wave.

1) Evaluation by F-Wave

When the peripheral nerve is electrically stimulated in a vigorous manner, the large wave that first appears on the monitor is called the M wave (the summation of muscle action potential), and the subsequent wave is called the F-wave. The F-wave is a compound action potential resulting from the innervated muscle by electrical stimulation. The F-wave is thought to appear as an excitatory stimulation transmitted through alpha motor neurons in a retrograde fashion and reignites after being

transmitted to the anterior horn cells in the spinal cord, before being transmitted again through the same alpha motor neurons in an antegrade fashion, with the consequence that an F-wave is recorded [37].

The F-wave can be recorded in various muscles, but excitation of neurons occurs only approximately once every 10–100 times. For this reason, if a surface electrode is used for recording, the excitation of several motor units is recorded in a single stimulation, and its latent time, amplitude, and waveform vary every time [37]. With regard to the F-wave that estimates the nerve conduction velocity and the excitability of spinal motor neurons, Tsai et al. [38] reported that the amplitude of the F-wave in patients with neurological sequelae of stroke correlates with the severity of spasticity. In this context, it is currently recommended as a noninvasive, quantitative, and neurophysiological examination of spasticity.

In general, patients with spasticity show an increase in F-wave amplitude, the F/M ratio (the ratio of the maximum M-wave amplitude and the mean F-wave amplitude which were derived from the same muscle), and the frequency of F-wave appearance (the ratio of F-wave to total number of stimulations). In patients with spasticity, the F/M ratio increases to 5 % of the maximum amplitude or more, occasionally to 10 % of it. The frequency of appearance of 80 % or more suggests a presence of spasticity caused by upper motor neuron disorders.

2) Evaluation by H-Wave

The H-wave, which was named after its discoverer Hoffmann, is the potential corresponding to the deep tendon reflexes and is regarded as a simple method to record spinal reflexes. The group Ia neural fibers, or the afferent nerves in the stretch reflex, are excited by electrical stimulation in antegrade manner, which generates an impulse and makes synaptic connections in the spinal cord. The postsynaptic potential then excites the motor nerves in the anterior horn cells in spinal cord. When its potential reaches the innervated muscle through alpha motor neurons, the H-wave is recorded.

However, the afferent nerves include the group Ia neural fibers that originate from the Golgi tendon organ. It is difficult to excite only the group Ia neural fibers in the muscle; therefore, the same waveform does not always appear in each stimulation [39]. In healthy adults, the muscles where the H-wave can be detected are limited to the quadriceps, soleus muscle, and flexor carpi radialis. However, the H-wave can also be detected in certain other muscles when performing a weak voluntary contraction.

It is known that patients with spasticity show an increase in the H/M ratio (the ratio of the maximum M-wave amplitude and the maximum H-wave amplitude that were derived from the same muscle). While an association with the severity of spasticity and the H/M ratio has not been found, it is believed that it helps objectively evaluate the time course of the same patient.

C. Effect of rTMS on Spasticity

rTMS is expected to regulate the excitability by providing stimulus to the cerebral cortex and to promote the smooth transmission of information signals between the upper central nervous system and the spinal cord. rTMS includes low-frequency rTMS, which is performed on the primary motor area in the nonlesional hemisphere, and high-frequency rTMS, which is performed on the primary motor area in the affected hemisphere. Both are recognized for their antispasticity effect.

1) Reports on High-Frequency rTMS

Centonze et al. [40] performed high-frequency rTMS at 5 Hz for 15 minutes (1 cycle consisted of 10 seconds of 5 Hz stimulation and 40 seconds of rest, in a total of 18 cycles) in the lower limb area of the primary motor cortex in the affected hemisphere of multiple sclerosis patients with lower limb spasticity. This was performed for 2 weeks, and MAS and the H/M ratio of the lower limb with spasticity were measured before and after the treatment.

As a result, high-frequency rTMS of 5 Hz instantaneously reduced the H/M ratio, with the reduction maintained also after performing daily treatment for 2 weeks. In accordance with this, the reduction of MAS was also observed after providing daily stimulation for 2 weeks. It was also confirmed that the reduction of both the H/M ratio and MAS was maintained for at least 1 week after the end of 2-week protocol.

Wupuer et al. [41] performed a total of 1000 pulses of high-frequency rTMS at 10 Hz (1 cycle consisted of 5 seconds of 10-Hz stimulation and 25 seconds of rest, in a total of 20 cycles) in the hand and finger area of the primary motor cortex in the affected hemisphere of patients with spasticity and neurological sequelae of stroke. The change in the F-wave was recorded before and after the treatment. Prior to the stimulation, the F-wave amplitude and F/M ratio in patients with neurological sequelae of stroke were significantly increased compared to those in healthy subjects. After performing high-frequency rTMS, however, the F/M ratio was significantly reduced.

These two reports suggest that high-frequency rTMS on the affected hemisphere eventually suppresses the excitability of the spinal cord. Therefore, we consider that it can be a therapeutic intervention for poststroke patients with upper limb hemiparesis.

2) Reports on Low-Frequency rTMS

Málly and Dinya [42] performed low-frequency rTMS and examined its effects in patients with stroke who had survived about 10 years after onset and had no change in the motor function for more than 5 years.

First, they performed single TMS on both hemispheres and classified the patients into four groups (Group A to D) according to the level of elicited upper limb movements. In Group A, rTMS was performed on both hemispheres (movements were elicited in both upper limbs). In Group B, rTMS was performed on the nonlesional hemisphere (movements were not elicited in either upper limb). In Group C, rTMS was performed on the affected hemisphere (movements were elicited only in the upper limb on the nonparalyzed side); and in Group D, rTMS was performed on the nonlesional hemisphere (movements were elicited only in the upper limb on the nonparalyzed side) (Table 2.17). Low-frequency rTMS 1 Hz, a total of 100 pulses (twice daily) was carried out on each stimulation site continuously for a week.

A reduction in spasticity was observed in each group 1 week after the treatment, and consequently the improvement continued for at least 1 month. Based on this, Málly and Dinya concluded that low-frequency rTMS can improve paralyzed limbs even if a patient has already reached a plateau state.

3) Reports by Our Group

It has been reported that NEURO-15 conducted by our group also has an antispasticity effect. Kakuda et al. [29] conducted NEURO-15 in poststroke patients with upper limb hemiparesis who have spasticity and assessed the degree of their upper limb motor function and upper limb spasticity before and after treatment. As a result, FMA and WMFT showed improvement in the motor function of the upper limb on the paralyzed side after 15 days of low-frequency rTMS and intensive OT. The reduction in muscle tonus in the upper limb flexors on the paralyzed side was also confirmed by the reduction in MAS.

Much of the mechanism by which rTMS brings about an antispasticity effect still remains unknown; however, we speculate that neural activation of the affected hemisphere can partly contribute. This is based on the finding that both high-frequency rTMS on the affected hemisphere and low-frequency rTMS on the nonlesional hemisphere reportedly increase the neural activity of the affected hemisphere and have anticonvulsant effects [40–42]. We consider that the increase in neural activities of the motor cortex of the affected hemisphere resulted in the increase in descending inhibitory input through the corticospinal tract, which suppressed the excitability of gamma and alpha motor neurons and reduced the spasticity of peripheral muscle (Fig. 2.17).

Table 2.17 Consideration by Málly and Dinya

Classification	Induction of movement	Stimulation sites
Group A	Observed in both upper limbs	Both hemisphere
Group B	Not observed in either upper limb	Non-lesional hemisphere
Group C	Observed only in the upper limb on the non-paralyzed side	Affected hemisphere
Group D		Non-lesional hemisphere

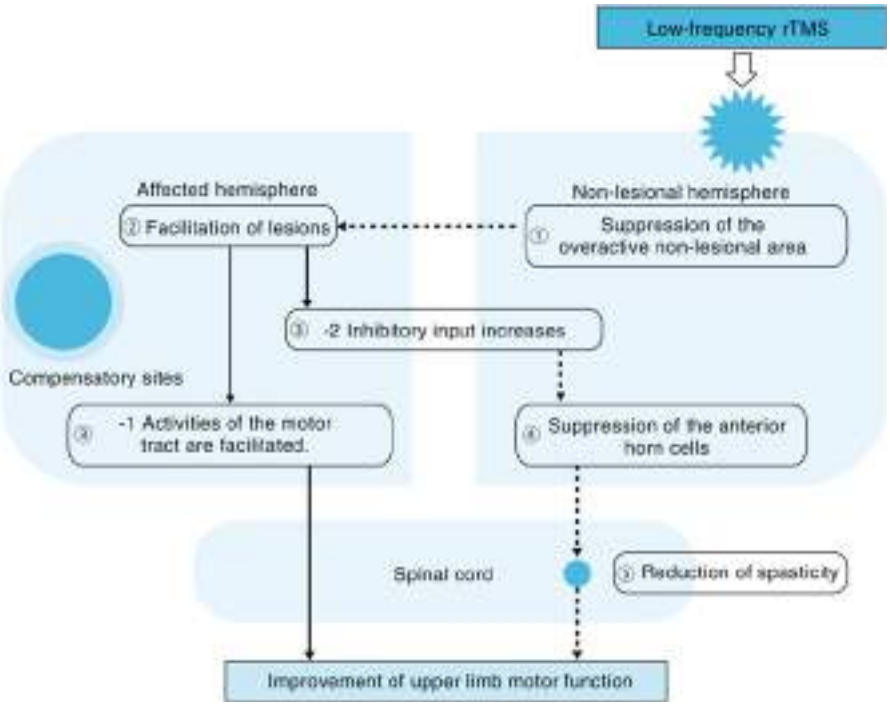

Fig. 2.17 Mechanism by which low-frequency rTMS brings about an anti-spasticity effect. Low-frequency rTMS on the non-lesional hemisphere increases the neural activity of the affected hemisphere, which promotes the activity of the motor system and results in a reduction of spasticity

Therefore, we conducted a study using the F-wave in poststroke patients to review the effects of low-frequency rTMS on the motor neuron excitability [43].

We examined 13 poststroke patients with upper limb hemiparesis who met all of our group's eligibility criteria of rTMS treatment (age: 57.5 ± 11.1 years old, elapsed time after onset: 55.2 ± 51.4 months, cerebral infarction: five patients, intracerebral hemorrhage: eight patients), after exclusion of those who received local injection of antispasticity drugs such as Botulinum Toxin Type A (BoNT-A).

The severity of the upper limb hemiparesis was assessed by using BRS for hand-fingers as a baseline. Among the study patients, seven patients were at stage IV, three patients were at stage V, and the other three patients were at state VI. The mean score of MAS was 0.62 ± 0.62 in the finger flexors and 0.73 ± 0.63 in the wrist flexors. Low-frequency rTMS at 1 Hz was applied on the hand finger area of the primary motor area in the nonlesional hemisphere of the study patients for 20 minutes. Before and after the treatment, the frequency of F-wave appearance and the F/M ratio were measured.

The results showed that, prior to the application of rTMS, the F/M ratio was significantly higher in the upper limb on the paralyzed side compared to that in the

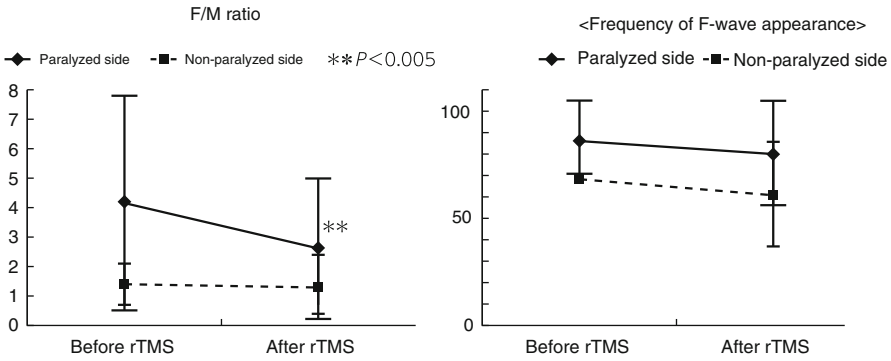

Fig. 2.18 Changes in the F/M ratio and the frequency of F-wave appearance by performing low-frequency rTMS. The F/M ratio of the upper limb on the paralyzed side was significantly reduced by low-frequency rTMS on the non-lesional hemisphere for 20 minutes [43]

upper limb on the nonparalyzed side. Low-frequency rTMS produced a downward trend in the frequency of F-wave appearance in the upper limbs both on the paralyzed and nonparalyzed side; however, its change was not statistically significant. A significant decrease in the F/M ratio was observed in the upper limb on the paralyzed side after the application of rTMS, while no significant change was observed in the upper limb on the nonparalyzed side (Fig. 2.18) [43].

This suggests that in poststroke upper limb hemiparesis, a pathological increase in the excitability of motor neurons controlling the upper limb on the paralyzed side can be improved. In other words, spasticity can be improved by applying low-frequency rTMS on the nonlesional hemisphere.

Furthermore, there is already a growing body of evidence that the motor function of the upper limb after stroke can be improved by rTMS. Based on our study, we consider that a reduction in spasticity partly contributes to the mechanism of the improvement. We expect that clinically applicable therapeutic intervention for spasticity will be conducted in the future, such as rTMS to enhance the excitability of the affected hemisphere.

6 Neuroimaging Studies of Patients with Upper Limb Hemiparesis

It is believed that rTMS directly influences the cerebral cortex to improve cerebral plasticity. In fact, however, it is still unclear how rTMS and rehabilitation influence plasticity and the functional reorganization of the cerebral cortex. Nonetheless, there are several reports which studied how rTMS and rehabilitation influence on the cerebral blood flow and measured the regional cerebral blood flow (rCBF) using

near-infrared spectroscopy (NIRS), single photon emission computed tomography (SPECT), positron emission tomography (PET), and other tools.

In this section, we will introduce some of these reports and describe our own report in which the effects were studied on the basis of a change in rCBF measured by SPECT after performing the 15-day protocol of rTMS and intensive OT during hospitalization (NEURO-15).

A. Report in Which rTMS Was Performed and the Change in rCBF Was Measured by NIRS

Hada et al. [44] measured the blood flow and aerobic metabolism of the cerebral cortex in 12 healthy right-handed subjects using NIRS during and after the performance of rTMS. rTMS was applied on the primary motor area of the left hemisphere controlling the right FDI muscle using a figure-8 coil. Simulation was given 10 times at 0.5 Hz, or 2 Hz and the intensity was 80 % or 120 % of the motor threshold at rest. NIRS probes were placed on the inside edge of the figure-8 coils at 3 cm intervals, and measurement was carried out directly under the stimulation site by the coils. As a result, during and after rTMS stimulation, reduction in the concentration of total hemoglobin (total-Hb) and oxygenated hemoglobin (oxy-Hb) as well as an increase in the concentration of deoxygenated hemoglobin (deoxy-Hb) were observed at stimulation intensities of both 80 % and 120 %. However, Hada et al. said that the mechanism remained unclear.

B. Report in Which rTMS Was Performed and the Change in rCBF Was Measured by SPECT

There are several studies that applied rTMS to healthy subjects and investigated the change in rCBF. One example is a study by Okabe et al. [45], who applied rTMS on the primary motor cortex of the left hemisphere in five healthy subjects and measured rCBF by ^{99m}Tc-ethyl cysteine dimmer (^{99m}Tc-ECD) SPECT. Okabe et al. used figure-8 coils and performed monophasic rTMS (1 Hz, 60 pulses/minute) below the motor threshold. Sham stimulation (fictitious stimulation) was also applied as a control. Radioactive isotopes were injected during stimulation, and the obtained SPECT imaging results were evaluated by using statistic parametric mapping (SPM) 99. As a result, an increase in rCBF was observed in the contralateral (right) cerebellum (Fig. 2.19) [45], while a decrease in rCBF was observed in the primary motor cortex, superior parietal lobule, inferior parietal lobule, dorsal and ventral premotor cortex, and supplementary motor area of the contralateral cerebrum (Fig. 2.20) [45].

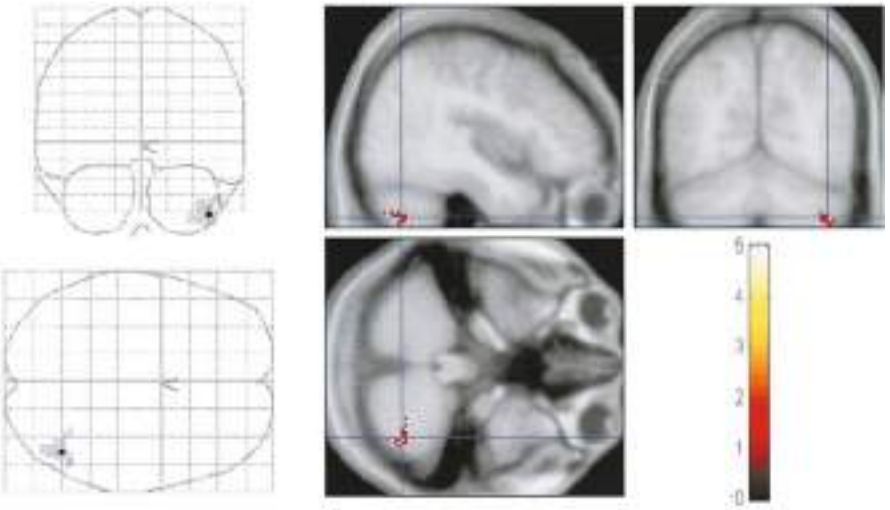

Fig. 2.19 Areas where rCBF increased. The areas where rCBF increased during rTMS on the primary motor cortex of the left hemisphere in comparison with those during the sham stimulation are shown. rCBF increased in the lateral portion of the right posterior cerebellar hemisphere, which is located on the opposite side of the rTMS applied area

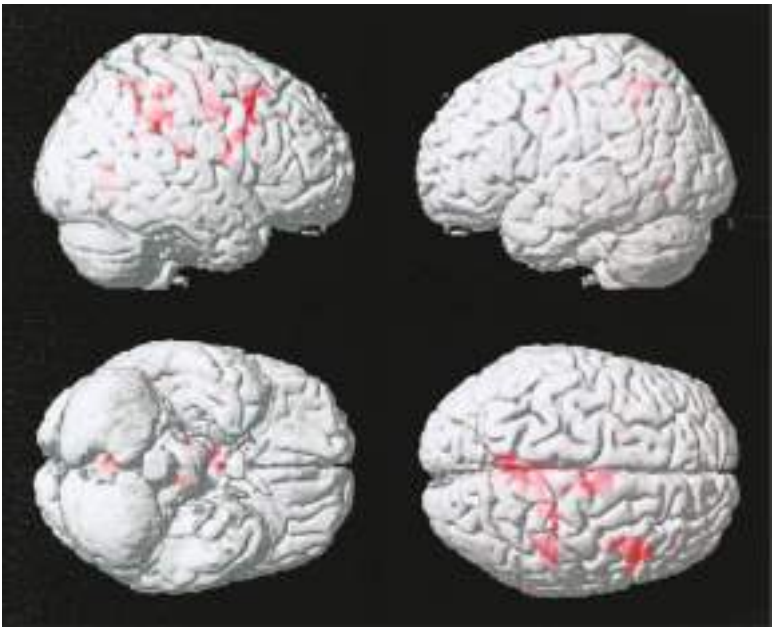

Fig. 2.20 Areas where rCBF reduced. During rTMS on the primary motor cortex of the left hemisphere, a significant decrease in rCBF was observed in the primary motor cortex (M1) including the hand and finger area, the dorsal premotor cortex (dPM), the ventral premotor cortex (vPM), the inferior parietal lobule (IPL) including supramarginal gyrus (Brodmann's area 40), part of the superior parietal lobule (SPL) and the supplementary motor area (SMA) of the right hemisphere. In the left hemispheric imaging, no significant rCBF changes were seen except a few areas over which rCBF decreases in the right hemisphere were projected through the brain

Based on these results, Okabe et al. concluded that low-frequency rTMS at almost same intensity as the motor threshold brings out a change in rCBF. It seems that the cerebellar hemisphere changes its activity in parallel with that of the contralateral primary motor cortex due to strong facilitatory connections between these two areas. Generally, a parallel change in rCBF is commonly known as crossed cerebellar diaschisis.

They consider that the decrease in rCBF in the primary motor cortex of the right hemisphere showed an interhemispheric inhibitory effect via the corpus callosum caused by activation of the primary motor cortex of the left hemisphere and the decrease in rCBF in the right parietal lobe, premotor cortex, and supplementary motor area indicated some secondary effects.

The dynamics of activation of neural activity are usually similar to that of an increase in rCBF and metabolism; however, an increase in rCBF in the motor cortex can be seen when neural activity is suppressed [46]. Therefore, their changes do not necessarily occur in a parallel manner. They mentioned that changes in neural activity may occur even when no change in blood flow was observed. The rCBF reflects the energy consumption, namely, metabolic activity of the vertebral cortex induced by the excitability or inhibitory synaptic activity of the cerebral cortex.

The effects of rTMS on the cortex are a mix of the excitatory and inhibitory neural firings, namely, the synaptic activities [47]. An increase in blood flow means a reduction in physiological activity of the cerebral cortex when it was caused by increased activity of inhibitory synapses.

On the other hand, Hosono et al. [48] made a comparison between monophasic and biphasic rTMS. They performed monophasic rTMS at 0.2 Hz and biphasic rTMS at 1 Hz, with 250 pulses for each, on the left premotor cortex of 7 healthy right-handed subjects (mean age ± SD: 32.7 ± 10.7 years old) using a figure-8 coil. Before and after each rTMS, SPECT was carried out and was tested by SPM2. The resultant increase in rCBF was observed at the stimulation site and its adjacent left frontal lobe (Brodmann's area 6) after monophasic stimulation at 0.2 Hz as well as in the left occipital lobe and right parietal lobe after the biphasic stimulation at 1 Hz. No increase was observed in the motor cortex (Fig. 2.21, Table 2.18) [48]. They said that, when applied to the premotor cortex, monophasic rTMS is more useful than biphasic rTMS. The possible reasons for the increase in rCBF in areas distant from the stimulation site are either that when biphasic stimulation at 1 Hz was applied the distant areas were influenced via corticocortical connections [49] or the stimulation is transmitted through the corpus callosum [45].

Relatively few studies have used rTMS for treatment purposes; however, Marcondes et al. [50] performed rTMS in tinnitus patients with normal hearing and performed SPECT examination before and after the stimulation. They randomized 19 patients into either the rTMS at 1 Hz group or the sham stimulation group. As control groups, subjects with normal hearing and patients with tinnitus received rTMS. Stimulation was given on the left temporal-parietal cortex for 5 days. ^{99m}Tc-ECD SPECT imaging was performed before and 14 days after rTMS and a comparison made of the Z score for each voxel before and after the stimulation by the *T*-test. As a result, a decrease in neuronal activity was observed in the left inferior temporal gyrus of the rTMS group.

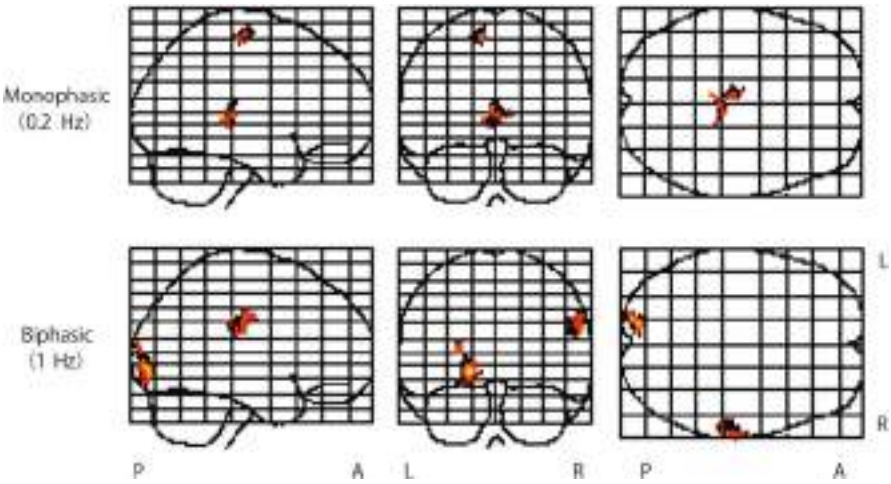

Fig. 2.21 Changes in rCBF by monophasic and biphasic rTMS. Figures shown by maximum intensity projection (MIP). They show the areas where rCBF increased after monophasic and biphasic rTMS on the premotor cortex

Table 2.18 Regional CBF increase after monophasic 0.2 Hz and biphasic 1 Hz rTMS over premotor cortex[a]

Group A	Condition of rTMS application	Brain area	Talairach coordinate			Z score
			x	*y*	*z*	
	Monophasic (0.2 Hz)	Left thalamus	0	−23	12	5.03
		Left frontal lobe (Brodmann's area 6)	−8	−11	58	4.27
	Biphasic (1 Hz)	Left occipital lobe (Brodmann's area 17)	−16	−84	−1	4.51
		Left occipital lobe (Brodmann's area 17)	63	−16	−6	3.99

Adapted from Ref. [48]

[a]Talairach coordinates and Z-scores of the sites which showed the maximum value are shown

C. Report in Which Intensive Rehabilitation Was Performed and Changes in rCBF Were Measured by SPECT

There is an interesting report that studied the changes in rCBF by performing SPECT before and after intensive rehabilitation. Könönen et al. [51] studied 12 chronic patients who were recruited after 6 months from the onset of cerebral infarction [mean age: 48 years old, mean time from onset: 36 months (7–132 months)].

Könönen et al. introduced the CIMT defined in the EXCITE study [52], which forces patients to use the paretic upper limb for 2 weeks (Fig. 2.22) [51], and measured rCBF at rest before and 2 weeks after the intervention by using ^{99m}Tc-ECD SPECT.

Fig. 2.22 A lightweight sling to constrain the hand-finger and upper limb on the non-paralyzed side. The accompanying watch can detect the patient's body temperature and measure how long he/she has worn the sling [51]

rCBF was tested by using SPM99 and MATLAB®. As a result, increased blood flow was observed in the precentral gyrus of the frontal lobe (Brodmann's area 6) and the superior frontal gyrus of the frontal lobe (Brodmann's area 10) in the affected hemisphere, in the superior frontal gyrus of the frontal lobe (Brodmann's area 6) and the cingulate gyrus (Brodmann's area 31) in the unaffected hemisphere, and on both sides of the cerebellum, while decreased blood flow was observed in the lingual gyrus (Brodmann's area 18) in the affected hemisphere (Fig. 2.23, Table 2.19) [51]. In the unaffected hemisphere, decreased blood flow was observed in the middle frontal gyrus of the frontal lobe (Brodmann's area 8 and 10), the fusiform gyrus of the temporal lobe (Brodmann's area 20), and the inferior temporal gyrus (Brodmann's area 37).

It is known that the superior frontal gyrus integrates information from multiple sensory organs and becomes prepared for movements, while the cingulate gyrus receives signals directly from the primary motor area. The cerebellum has a role in coordinating skilled voluntary movements and is involved in regulating muscle tone and posture. In CIMT, increased blood flow was observed in the area associated with the motion control over the affected side.

D. Report in Which Finger-Tapping Movement Was Performed and Changes in rCBF Were Measured by PET

There is a report that examined changes in rCBF by using PET. Carey et al. [53] investigated the correlation of the evaluation results of upper limb motor function and changes in rCBF measured by PET in nine right-handed stroke patients (seven men, mean age ± SD: 72.0 ± 9.8 years old). Carey et al. assessed the upper limb motor function by ARAT twice: at 2 to 7 weeks after stroke onset (subacute phase) and at 6 months after onset, and they used PET to measure the rCBF when the

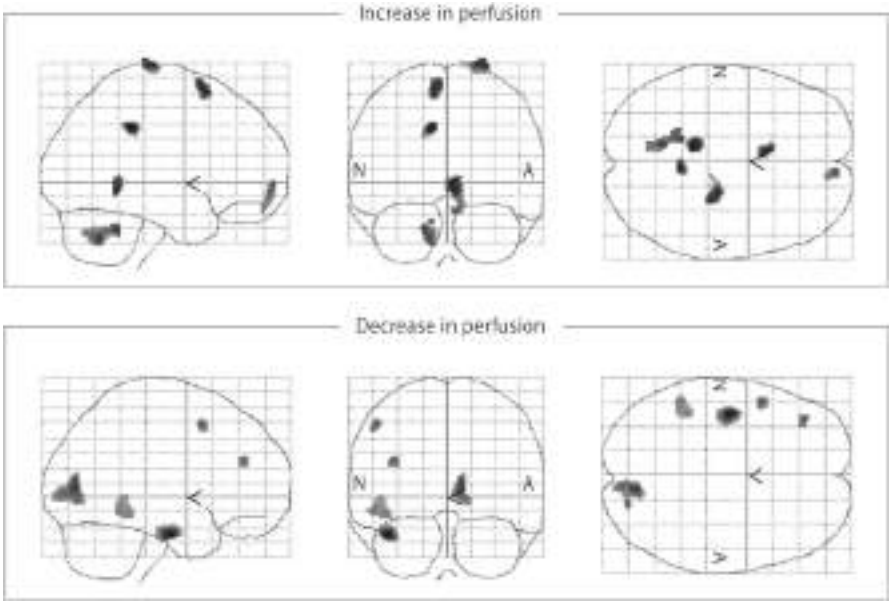

Fig. 2.23 Changes in perfusion by CIMT. The cerebral areas with changed perfusion are shown. The diagrams in the *upper row* show the area where perfusion increased and the diagrams in the *bottom row* show the areas where perfusion decreased. The letter As in the figures show the affected hemisphere and the letter Ns show the non-lesional hemisphere (Adapted from Ref. [51])

Table 2.19 The cerebral areas with changed perfusion in SPECT after two weeks of CIMT

Anatomical area	Perfusion change[a]	Brodmann's area	Size (voxels)	Talairach coordinates[a]			*z*-score[c]
				x	*y*	*z*	
Superior frontal gyrus	+	10	54	8	60	−5	2.97
	+	6	65	−8	18	56	3.24
Precentral gyrus	+	6	67	22	−18	76	3.28
Cingulate gyrus	+	31	65	−10	−35	37	3.57
Cerebellum	+	–	120	−16	−46	−26	3.10
	+	–	54	4	−47	−3	3.26
Medial frontal gyrus	–	10	24	−38	40	20	3.34
	–	8	27	−50	12	46	3.24
	–	20	145	−42	−13	−21	4.61
Inferior temporal gyrus	–	37	111	−50	−45	−7	3.00
Lingual gyrus	–	18	187	10	−75	9	3.77

Adapted from Ref. [51]

[a]+ denotes increased perfusion, – denotes decreased perfusion

[b]A negative value on the x-axis in the Talairach's coordinates denotes the unaffected hemisphere, and a positive value denotes the affected hemisphere

[c]z-score of *t*-test

patient does a simple finger-tapping movement. SPM99 was used for the test. The results showed that in the subacute phase, the linear correlation between changes in the upper limb motor function and movement-related rCBF was observed in the supplementary motor area, the cingulate gyrus of both hemispheres, the insular cortex of the unaffected hemisphere, and the small area of the primary sensory motor area of the affected hemisphere. On the other hand, at 6 months after onset, the corresponding regions were limited mainly to the primary sensory motor area of the affected hemisphere spreading beyond the cingulate gyrus. The authors indicated that the recovery of movement was correlated with the decreased activity of the unaffected hemisphere and the increased activity in the primary sensory motor cortex of the affected hemisphere.

E. Our Study Investigating the Development of Functional Reorganization with rTMS and Rehabilitative Intervention Using Neuroimaging Assessment

The combination therapy of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the nonlesional hemisphere and rehabilitation significantly improves the motor function of patients with upper limb hemiparesis after cerebral infarction. We studied the recovery mechanism using a functional magnetic resonance imaging (fMRI) (1). In this study, we conducted medical interventions in 47 patients with upper limb hemiparesis after cerebral infarction through 15-day hospitalization therapy. Before and after the intervention, fMRI was measured under exercise stress and the laterality index calculated by considering the number of the activated voxels of Brodmann's area 4 and 6 (the laterality index ranged from −1 to 1). Among the subjects who were divided into two groups based on fMRI findings before the intervention, a significant increase in the laterality index was observed after intervention in the patient group which showed an activation in both cerebral hemispheres ($n=27$) ($P<0.05$), and the activation shifted to the lesional hemisphere [63]. On the other hand, a significant increase in the activity of the lesional hemisphere was observed in the patient group which showed an activation in only one of the cerebral hemispheres ($n=20$) ($P<0.05$) [63]. It was suggested that the intervention induced the functional cerebral cortex to be restructured, which may have led to the upper limb motor function recovery on the paralyzed side (1).

We also conducted another study with 33 patients with upper limb hemiparesis after stroke. In this study, the relevant cerebrocortical areas were examined before and after the intervention with rTMS and the intensive occupational therapy by considering the correlation of the change in the upper limb motor function and the change in the regional cerebral blood flow (2). We used FineSRT to perform SPECT to measure the regional cerebral blood flow with 99mTc-ECD and measured the blood flow levels in 46 regions corresponding to the individual gyrus which subdivided the region of interest (ROI). In addition, the ROI analysis was conducted over

six major Brodmann's areas. The asymmetry indices (AIs) were calculated in 52 regions [64] using the average of the right and left ROI and the correlation examined between the change in the AIs and the differences in the Fugl-Meyer Assessment (FMA) before and after the intervention. As a result, out of the 52 regions, a significant correlation was observed in the superior frontal gyrus and the middle frontal gyrus [64]. It was suggested that the improvement of the upper limb motor function by FMA was associated with the improvement of the regional cerebral blood flow of the superior frontal gyrus and the middle frontal gyrus (2).

F. Our Report in Which rTMS Was Performed and Changes in rCBF Were Measured by SPECT

There have been no studies reporting the effects of rTMS on poststroke patients based on changes in rCBF measured by SPECT. Thus, we examined how our ongoing NEURO-15 influences a patient's brain and has an effect on the plasticity and the functional reconstruction of the cerebral cortex [54].

1) Study Patients

Of the poststroke patients with upper limb hemiparesis who met all the eligibility criteria of NEURO-15, we studied 17 inpatients in our department (Jikei University Hospital) in whom SPECT could be retrospectively performed at the time of admission and at 4 weeks after discharge. The clinical background of the study patients is shown in Table 2.20; the mean age at the time of intervention was 56.0 ± 10.2 years old (23–67 years old) and the mean time from onset to intervention 56.9 ± 39.4 months

Table 2.20 Clinical background of the study patients

Age at the time of intervention (years old)		56.0 ± 10.2
Male/female		12/5
Subtype of stroke	Cerebral infarction	4
	Subcortical hemorrhage	10
	Putaminal hemorrhage	1
	Thalamic hemorrhage	2
Dominant hand/paralyzed hand	Right/right	13
	Right/left	3
	Left/left	1
BRS (median)	Hand-finger	Stage IV
	Upper limb	Stage IV
Time from onset to intervention (months)		56.9 ± 39.4

(17.5–134.3 months). The subtypes of stroke of the study patients included four cerebral infarctions, ten subcortical hemorrhages, one putamen hemorrhage, and two thalamic hemorrhages. The affected area varied from patient to patient; however, none of them brought about obstacles when making an analysis by SPM5. The affected areas included 13 left hemispheres and 4 right hemispheres, or 14 upper limbs on the dominant hand side and 3 upper limbs on the nondominant hand side.

The median BRS at the time of intervention was Stage IV for both the upper limb and hand-finger. This study was conducted with the approval of the ethics committee of our university. We obtained informed consent from all patients.

2) Treatment Protocol

The treatment protocol consisted of the low-frequency rTMS and intensive OT based on the NEURO-15. One session of low-frequency rTMS at 1 Hz lasted for 20 minutes (1200 pulses). The intensive OT as a combination therapy lasted for 120 minutes, which was conducted daily (two sessions daily) except on the morning of the admission day and Sunday. A total of 23 sessions were conducted over 15 days. Similar to NEURO-15, the stimulation site was the primary motor area of the unaffected hemisphere and the intensity set at 90 % of the motor threshold. Upper limb-related items in FMA and the performance time of 15 tasks in WMFT were used to evaluate the upper limb motor function. SPECT and the upper limb motor function test were performed before intervention (immediately after admission and 4 weeks after discharge).

3) Examination and Analysis by SPECT

SPECT examination was performed in patients at rest and with their eyes closed, by using ^{99m}Tc-ethyl cysteine dimmer (^{99m}Tc-ECD) as a tracer. Intravenous 600 MBq of ^{99m}Tc-ECD was administered to patients at rest and with their eyes closed and the images taken 20 minutes later. SPECT was analyzed using SPM5 [55, 56]. After the images of patients whose right hemisphere was affected were inverted, the analysis was performed and all of them considered as left hemisphere lesions. A paired *t*-test was used for an image analysis at the time of admission and 4 weeks after discharge.

4) Results

All 17 study patients completed the 15-day treatment protocol, and no adverse events and adverse reactions were observed during hospitalization. No patient experienced any adverse events or adverse reactions during 4 weeks from discharge. With regard to the changes in the evaluation of upper limb motor function before and after intervention, upper limb-related items in FMA showed a significant increase from 42.76 ± 11.97 points (mean ± SD) to 45.52 ± 11.38 points ($P < 0.001$) and the performance time of 15 tasks in WMFT a significant decrease from 3.18 ± 1.18 to 2.64 ± 1.38 ($P < 0.001$). A significant increase in rCBF was observed

in the insular cortex (Brodmann's area 13), the precentral gyrus (Brodmann's area 44), the cerebellum in the affected hemisphere, and the tongue gyrus (Brodmann's area 18) and the cerebellum in the unaffected hemisphere. A decrease in rCBF was observed in the middle frontal gyrus (Brodmann's area 6), the precentral gyrus (Brodmann's area 4), and the posterior central gyrus (Brodmann's area 3) in the unaffected hemisphere (Fig. 2.24). The Talairach coordinates and Z-score of each area are as shown in Table 2.21.

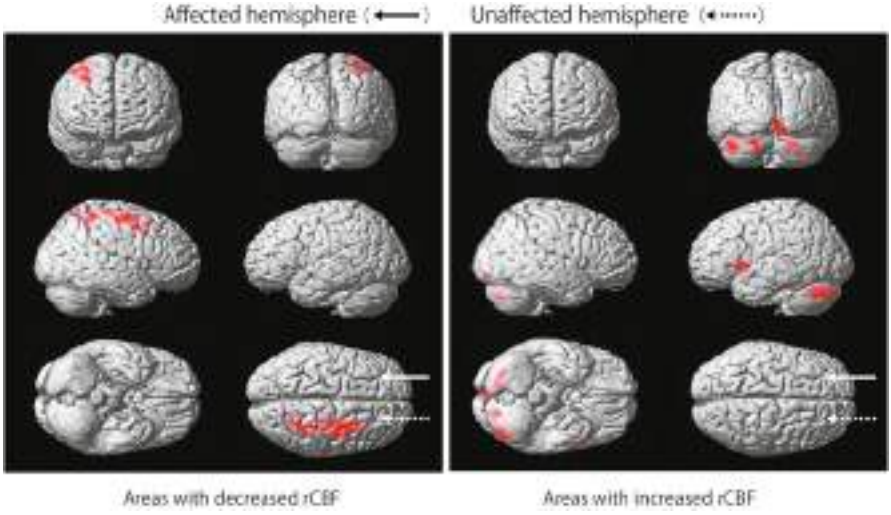

Fig. 2.24 Areas with relative increases and decreases in local cerebral blood flow

Table 2.21 Areas where perfusion changes were observed before and after rTMS intervention

Area of brain	Area of brain	Perfusion change			Brodmann's area	Z score
		x	*y*	*z*		
Left insular cortex	+	−40	10	−4	13	5.90
	+	−45	8	1	13	5.41
Left precentral gyrus	+	−54	13	8	44	5.33
	+	−45	−66	−33	–	6.43
Left cerebellum	+	−18	−81	−31	–	6.16
	+	−16	−72	−35	–	5.99
Right lingual gyrus	+	3	−92	−12	18	6.64
	+	4	−85	−13	18	5.97
Right cerebellum	+	6	−80	−19	–	5.75
	+	25	−72	−33	–	6.31
	+	29	−65	−41	–	6.15
Right middle frontal gyrus	–	28	2	45	6	7.62
Right postcentral gyrus	–	20	−32	59	3	7.28
Right precentral gyrus	–	33	−20	52	4	6.73

5) Discussion

Imaging comparison studies before and after CIMT by SPECT, such as the report by Könönen et al. [51] described above, which were conducted to expect changes in the plasticity of the cerebrum, showed an increase in rCBF mainly in the precentral gyrus and the frontal gyrus in the affected hemisphere, while a decrease in rCBF was observed in the medial part, fusiform gyrus, and inferior temporal gyrus of the frontal lobe in the nonlesional hemisphere. This is similar to our research results. Swayne et al. [57] suggested that in chronic stroke the established imbalance of interhemispheric inhibition and additional inhibitory stimulus from the unaffected hemisphere might inhibit the establishment of the plasticity of the affected hemisphere. This study suggested that the increase in rCBF in the precentral gyrus (Brodmann's area 44) and its adjacent insular cortex (Brodmann's area 13) in the affected hemisphere might have meant that low-frequency rTMS and intensive OT relieved the imbalance of interhemispheric inhibition and improved the activity of the affected area and its surrounding area.

Furthermore, in this study, a significant increase in rCBF was observed in the lingual gyrus of the unaffected hemisphere. It delivers visual information from the V1 region of the visual association area to its subregion. In particular, the V2 region is an area where visual information is delivered separately into the dorsal stream and the ventral stream [58] and is a major transit point for visual information.

In particular, the dorsal stream delivers information to the middle temporal gyrus, the premotor area, and the premotor cortex and plays a major role in planning and conducting movements. In other words, the study results suggest that there is a possibility that low-frequency rTMS and the intensive OT brought about a change in rCBF in the cerebrum and the areas that are responsible for planning and conducting movements were activated, which resulted in an increase in rCBF in the lingual gyrus.

One of the limitations of this study was that self-exercise in the intensive OT varied from patient to patient. For this reason, each patient did not necessarily have an improvement in the plasticity of the cerebral cortex in the identical area through exercise. Secondly, this study was not an RCT that included a control group but included the intervention group only. We consider that it is necessary to verify the effects of low-frequency rTMS on rCBF and the effects of the intensive OT on rCBF independently. However, they have yet to be verified because there are problems with patient consent and the number of cases to obtain. In addition, this study had an issue in that the increase in rCBF in the affected hemisphere was observed only in the precentral gyrus and the insular cortex. A previous report indicated that the premotor area and the supplementary motor area may also play an important role in improving plasticity after stroke and in reorganizing the network [59]; however, the same results were not obtained in our study. For this reason as well, we believe that there is a need to examine a larger sample size.

7 Future Challenges

To date, we have worked with more than 1800 patients in our institution and our 9 associated institutions. The effectiveness was demonstrated in the multicenter study including 204 patients described above (p. 35) as well as in the multicenter study including as many as 1008 cases that is currently being submitted. In addition, international research papers are increasingly being published as a result of the sufficient recognition of rTMS as an effective treatment for neurological sequelae of stroke. The future challenges based on the results obtained from NEURO will be described below.

A. Timing to Perform rTMS

Our department started a combination therapy of low-frequency rTMS on the unaffected hemisphere and the unique intensive OT in poststroke patients with upper limb hemiparesis in April 2008, which was called the "six-day protocol." After confirming its safety, we started performing an extended "15-day protocol" named NEURO-15 in April 2009. This is a treatment in which low-frequency rTMS, which has an inhibitory effect of neural activity in local brain areas, is applied on the unaffected hemisphere, which reduces interhemispheric inhibition between the unaffected and the affected hemisphere, makes the affected hemisphere free from inhibition, and leads to a recovery in upper limb motor function. The eligibility criteria of NEURO-15 stipulate that a patient should be enrolled after 1 year from onset. In NEURO, the magnetic stimulation device that is originally not a therapeutic instrument but testing equipment is used as a therapeutic instrument after obtaining a patient's consent as well as the approval of the ethical committee of each institution. We therefore believe that NEURO-15 should be applied only in patients who are in a safer or more stable condition. Consequently, to date, NEURO has been conducted safely as we expected.

However, a report using a functional MRI (fMRI) in the subacute or acute stroke showed that activation of the unaffected hemisphere occurs at 3 months after onset or later [60]. Based on this fact, if rTMS treatment is performed in acute stroke, high-frequency rTMS on the affected hemisphere might be more effective. In fact, Sasaki et al. [61] conducted RCT that included 29 patients who were enrolled within 29 days after onset and divided them into the following 3 groups: high-frequency rTMS of 10 Hz group (1000 pulses in 10 minutes), low-frequency rTMS of 1 Hz group (1800 pulses in 30 minutes), and sham stimulation group. Comparing the results before and after the intervention, both the high-frequency and the low-frequency rTMS groups showed a significant increase in grip strength and tapping number. However, a statistically significant increase compared to the sham stimulation group was observed only in the high-frequency rTMS group (Fig. 2.25) [61].

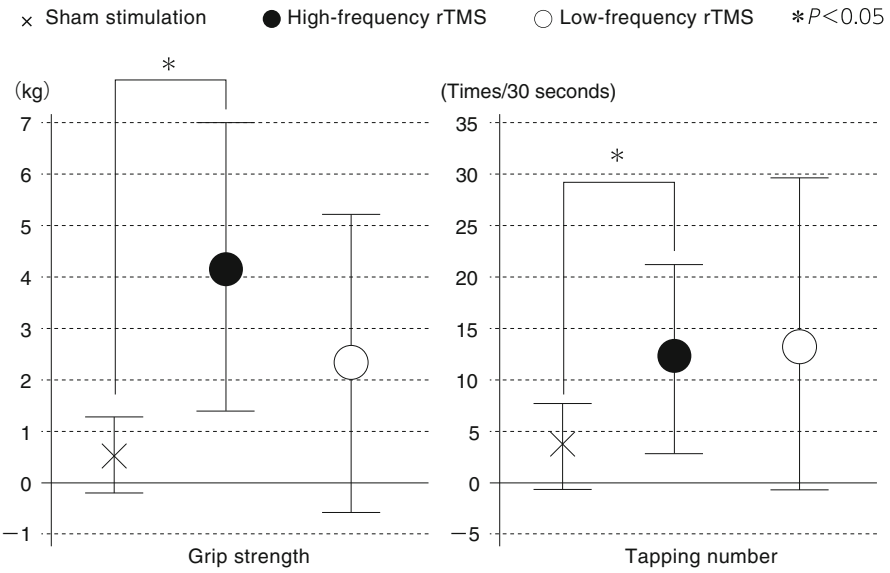

Fig. 2.25 Changes in grip strength and tapping number in three groups before and after intervention. The values are expressed as mean ± SD. Statistical analysis was performed by the unpaired *t*-test [61]

On the other hand, a report showed that stronger interhemispheric inhibition was observed in patients with poorer recovery of motor function after stroke [62]. Therefore, it is speculated that low-frequency TMS on the unaffected hemisphere is optimal for patients beyond 3 months from onset and whose motor function has been poorly recovered. We believe that the optimal timing of rTMS intervention and eligible patients for rTMS treatment should be determined based on its therapeutic properties after further consideration of rTMS.

B. Parameters of rTMS

For the challenges, see Chap. 7, section “Clinical Introduction of Other Stimulation Modalities” (p. 164).

C. Challenges with Rehabilitation Programs

Symptoms of patients with stroke range widely, therefore it is important to offer an approach appropriate for the symptoms as well as rehabilitation appropriate for changes in neural function brought about by rTMS. For this purpose, we must

accurately assess the patient's physical function and higher brain function and further understand the effects of rTMS. Based on these factors, we should understand the patient's needs and demands and set up a strategy to achieve them.

What is important here is which should be emphasized, namely, "the upper limb function exercise" including gross motor and dexterity movements or "the combined movements exercise" including bimanual operations such as ADL and object manipulation training. Even if the upper limb motor function is sufficient, an ideal pattern of target movement cannot be immediately achieved if the exercise program has not been adequately established. In addition, if a patient with insufficient upper limb function works on a target movement exercise, he/she may not be able to achieve an ideal pattern of target movement since an exercise program with compensatory patterns is followed. Therefore, as shown in Fig. 2.26, it is necessary to adjust the balance between "the upper limb function exercise" and "the combined movements exercise" along with the motor function improvement due to rehabilitation.

However, if a patient continues to avoid use of the upper limb on the paralyzed side in ADL because of its immobility, the activation of the affected hemisphere can be inhibited due to learned nonuse. Therefore, such a patient should use the upper limb on the paralyzed side in ADL as much as possible from an earlier stage, such as putting the upper limb on the paralyzed side on the table during a meal and cleaning the floor with a rag using both hands, as well as rolling over and getting up without using the handrail if the trunk is unstable (including movements starting from the paralyzed side).

It has already been reported that NEURO-15 enables a patient to reacquire not only the upper limb motor function on the paralyzed side but also movements in ADL. There are no reports to date that showed movements in ADL can be reacquired by conducting rTMS alone; however, there is a possibility that rTMS can enhance motion learning. Thus, further studies should be conducted in the future.

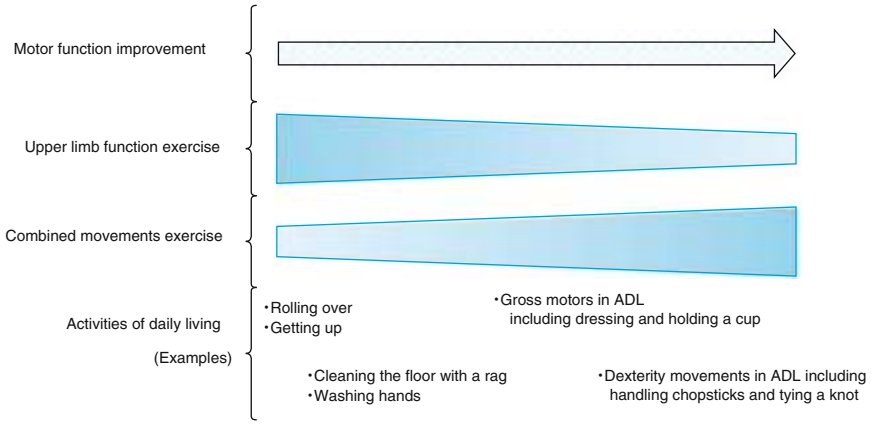

Fig. 2.26 Balance between "the upper limb function exercise" and "the combined movements exercise" along with the motor function improvement

D. Disparity of the Technical Level among Therapists and Differences of Rehabilitation Approach

Rehabilitation techniques greatly vary depending on the individual patient as well as the institution. The directions of rehabilitation also differ from each other: some focus on the functional improvement of the upper limb on the paralyzed side, while others focus on the acquisition of ADL movements by the nonparalyzed side. However, NEURO is a new treatment that can improve the upper limb function on the paralyzed side in a short period of time, which to date has been considered unable to be improved. Therefore, in NEURO, it is necessary to accurately evaluate a patient's function, which continually changes from day to day, and to adjust the rehabilitation approach depending on the situation. Therapists and physicians must fully understand the mechanism of NEURO and maintain advanced skills and high aspirations.

All institutions currently conducting NEURO are our associated institutions that had received and passed through the training at Jikei University School of Medicine. Medical staff at our department continue to provide them with direct instruction. Thus, these nine institutions can provide almost the same effect to patients receiving NEURO. Moreover, we have a system for exchanging information as needed online, and to share data. We also hold an annual workshop, which enables us to continue to develop through friendly competition among institutions.

In recent years, facilities other than our associated institutions have started applying a rehabilitation approach by reference to NEURO, although a lack of understanding about NEURO, ambiguous inclusion criteria, an obvious skill shortage of therapists, and other issues remain. We therefore decided to introduce a training system in consultation with our associated institutions for the purpose of obtaining the same effect in any facility.

This training is intended for institutions that will be introducing NEURO-15 in the future and consists of the direction of rehabilitation, basic learning about the disease, rehabilitation knowledge and skills, and the study of rTMS. After an institution completes the training, we take into account the reported results for a certain number of patients and determine if we can approve them as a NEURO providing institution. We believe that this process enables all NEURO providing institutions to improve their technical level and enables patients to receive treatment at the same level at any institution. Currently, the training session for NEURO-15 introduction is being held at Jikei University Hospital (Tokyo, Japan).

E. Application to Sensory Disturbance

Quite a few patients who wish to receive NEURO-15 have sensory disturbance. Sensory information is transmitted to the brain through the spinal cord and other nerves after sensory receptors receive not only visual and auditory information but

also information input from a certain part of the body. Information transmitted to the brain is integrated with a variety of information such as the current physical and mental condition, memory information, and the property of an object and leads to cognition and action. This process enables a person to keep the body in balance consciously or unconsciously, to understand the name of an object, and to move an object to where it should be.

Patients with stroke are often directed to work on upper limb motor function training with an awareness of the joint movement, muscle tone, and others. This training helps to increase the various kinds of selected information about the site and the movement, to activate the brain, and to facilitate the activity of the neural sprouting and unmasking, which results in improvement of upper limb motor function. With a sensory disturbance, however, information cannot be properly input, or if it has been input, it cannot be perceived, and the patient cannot be aware of the movement, which brings about sensory ataxia or motor learning impairment. With regard to the therapeutic effect of NEURO-15, it has been reported that patients with sensory disturbance show poorer improvement in the upper limb motor function on the paralyzed side compared to patients without sensory disturbance. In addition, patients cannot be aware of the therapeutic effects even after they have been obtained and cannot easily feel a sense of satisfaction. We think there is a need to review the stimulation site, intensity, and methods when performing rTMS in patients with sensory disturbance or to consider an entirely different approach in the future.

F. Application to Higher Cerebral Dysfunction

In recent years, researchers have started studying a new treatment using rTMS for higher brain dysfunction. Our department has been working on aphasia in particular and has performed inpatient treatment that is a combination treatment of low-frequency rTMS and speech training. However, research into attention disorders, memory impairment, apraxia, and agnosia remains insufficient.

Higher brain dysfunction varies depending on the part of the brain that has been injured. For example, when the parietal lobe is damaged, ideational apraxia, constructional apraxia, and hemispatial neglect (hemispatial agnosia) may occur. Aphasia, memory impairment, and auditory agnosia may occur when the temporal lobe is injured; visual agnosia, prosopagnosia, and Balint's syndrome may occur when the occipital lobe is injured; and executive dysfunction, attention disorders, and affective disorders may occur when the frontal lobe is injured. That is, since the symptoms vary depending on the injured area, it is necessary to determine which area is injured and to understand which pathway is inhibited by the injury, such as in commissural, association, or projection fibers, and which area is being used to compensate it.

Based on the understanding of the process described above, rTMS can finally be performed. Ultimately, however, it is extremely hard to determine which area is being used for a compensatory function. While it is possible to examine it using

fMRI or other methods, a patient must exactly understand the examiner's instructions and perform the procedure. Quite a few patients with higher brain dysfunction have difficulty in maintaining attention or cannot exactly perform a movement as directed because of impaired comprehension. Therefore, we consider that it is necessary to investigate techniques that enable us to grasp the compensatory area and the stimulating methods of rTMS even in these patients. Higher brain dysfunction is not yet properly understood outside the healthcare sector, and patients may be forced to leave their employment and suffer from a mental illness such as depression because of troubles in social relationships or at work. In addition, most insurance policies do not cover higher brain dysfunction as a special case of premium payment exemption. This creates difficulties for countless patients with higher brain dysfunction. Future research is imperative so that rTMS can be a ray of hope for patients with higher brain dysfunction.

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Chapter 3
rTMS for Poststroke Aphasia

1 Pathology and Current Status of the Treatment

A. Classification of Aphasia

Aphasia is defined as "condition characterized by impaired expression and comprehension of language representation resulted from post-lingual damage to the language center of the cerebrum due to some causes." While articulation disorders are caused by impaired exophasia (motor speech disorder), aphasia is considered to correspond to impaired endophasia (impairment of the language center of the cerebrum). The most frequent cause of aphasia is stroke, which accounts for approximately 90 % of all cases of aphasia, and followed by head injury. The major subtypes of stroke are a middle cerebral artery stroke and putaminal hemorrhage.

In more than 90 % of right-handed individuals and 60–70 % of left-handed individuals the language center is located in the left hemisphere, and the inferior frontal gyrus of the frontal lobe (Brodmann's areas 44 and 45), which is called Broca's area, and the superior temporal gyrus of the temporal lobe (Brodmann's areas 41 and 42), which is called Wernicke's area, are considered to correspond to the language center (Fig. 3.1).

Aphasia is classified into some types depending on the language function that is impaired. In case of damage to the Broca's area, typically patients present with "motor aphasia (Broca's aphasia)," namely, their auditory comprehension is maintained but spontaneous speech and handwriting are impaired, whereas in case of damage to the Wernicke's area, spontaneous speech is fluent but auditory comprehension is impaired, and patients present with "sensory aphasia (Wernicke's aphasia)," which is associated with paraphasia.

Other relatively common types of aphasia include global aphasia following extensive damage to the frontal lobe (both auditory comprehension and spontaneous

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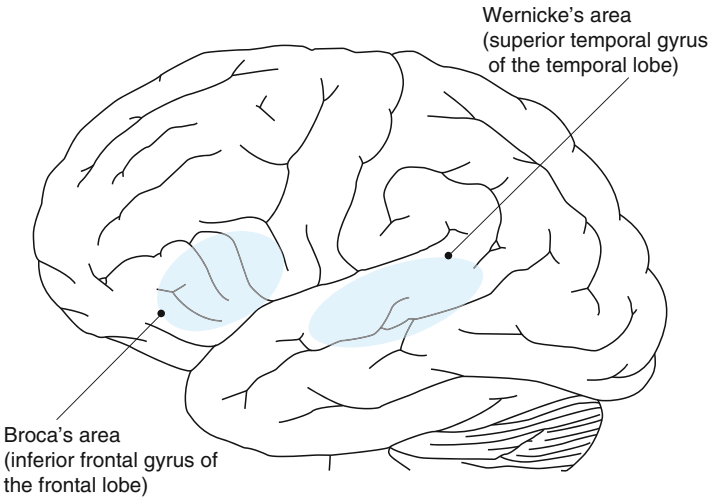

Fig. 3.1 Location of the language center. The language center is located in the frontal and temporal lobe of the human brain

speech are severely impaired), amnesic aphasia (the ability to name objects is severely impaired), and conduction aphasia (speech repetition is severely impaired).

B. Aphasia and Rehabilitation

The history of rehabilitation for the treatment of poststroke aphasia is by no means short, and training methods such as Schuell's systematic stimulation and facilitation method, the deblocking method proposed by Weigl, and functional reorganization method proposed by Luria are widely known [1]. In the "Japanese Guidelines for the Management of Stroke 2009," [2] "intensive and professional speech and language therapy (ST) for the treatment of aphasia from an early time point after stroke onset" is recommended with Grade B evidence. However, at present no firm evidence on the beneficial effects of these training methods has been accumulated yet.

On the other hand, based on our vast experience with the treatment of patients with aphasia, we have the impression that "compared to motor paralysis, in case of post-stroke patients with aphasia, the potential for recovery is sustained over a long period of time." More specifically, in the case of poststroke aphasia, the therapeutic window for rehabilitation intervention is wide, and we think that even in patients of chronic aphasia for several years after stroke, there is a possibility that language function will recover by conducting appropriate rehabilitation. This opinion has become the basis of our attempts to treat chronic poststroke aphasia through active therapeutic intervention.

2 Low-Frequency rTMS of the Right Frontal Lobe

In fact, the first time that rTMS was reported to have been used as therapeutic intervention of poststroke patients with aphasia was by the group around Naeser et al. [3] from Boston University. However, prior to this attempt by Naeser et al., Belin et al. [4] and Rosen et al. [5] had reported overactivity in the right frontal lobe of patients with aphasia resulting from impairment of the left frontal lobe and had interpreted this overactivity in the right frontal lobe as a maladaptive response that causes an extensive interhemispheric inhibition of the left hemisphere, thus preventing the compensation of language function through the left hemisphere.

Based on these reports, Naeser et al. [3] thought that it might be possible to reduce the extensive interhemispheric inhibition of the left hemisphere by means of low-frequency rTMS stimulation, which has an inhibitory effect on the unusually high activation levels in the right frontal lobe, and that this eventually might lead to the release of the left frontal lobe from interhemispheric inhibition, thus activating its compensatory role in language function (Fig. 3.2). In 2005 Naeser et al. [6] reported about a pilot study that involved four poststroke patients with motor aphasia resulting from lesions in the left frontal lobe, due to a stroke 5–11 years ago.

Naeser et al. treated these patients by applying 1-Hz low-frequency rTMS every day for 20 minutes (a total of 1200 pulses) over a period of 10 days to the inferior frontal gyrus of the right frontal lobe, which is located just contralateral to the Broca's area. As a result, it was found that directly after 10 days of rTMS the patients were able to recall the name of more objects than before treatment, and also

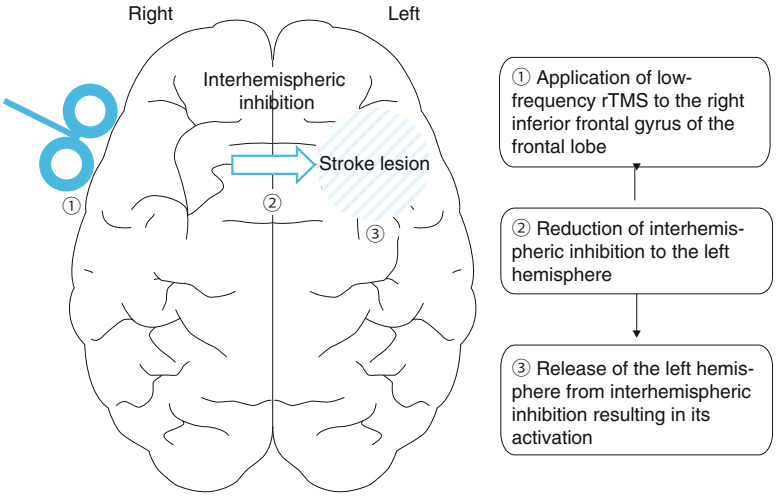

Fig. 3.2 Treatment concept of Naeser et al. The reduction of the interhemispheric inhibition to the left hemisphere by suppressing overactivity in the right hemisphere leads to the release of the left hemisphere that takes in a compensatory role in language function from inhibition, which in turn results in its activation

other improvements were observed, such as that the time required to recall the name of these objects had shortened. Moreover, these improvements were confirmed to have maintained also 8 months after conducting rTMS.

This study suggested that the application of low-frequency rTMS to the right frontal lobe for the treatment of aphasia resulting from lesions in the left frontal lobe might become a therapeutic intervention, and also hereafter there were continuous reports that confirmed the usefulness thereof.

Barwood et al. [7] divided 12 patients with aphasia resulting from lesions in the left frontal lobe into 2 groups. One group was treated with low-frequency rTMS to the right frontal lobe, and the other group was treated with sham stimulation to the same site for 10 days. As a result, it was found that in the low-frequency rTMS group language functions such as the ability to name objects had significantly improved compared to the sham stimulation group. Moreover, Weiduschat et al. [8] compared in a similar fashion the degree of improvement of language functions between a group treated with low-frequency rTMS to the right frontal lobe and a sham stimulation group. As a result, after 2 weeks of stimulation the improvement of language functions was significantly better in the low-frequency rTMS group. In addition, in the report by Weiduschat et al. positron emission tomography (PET) scans taken over time confirmed that neural activity in the left hemisphere had increased as a result of low-frequency rTMS to the right frontal lobe.

3 Importance of the Right Hemisphere for Compensating Language Function

Low-frequency rTMS to the right frontal lobe for the treatment of aphasia resulting from impairment of the left frontal lobe as proposed by Naeser et al. [3, 6] is based on the assumption that primarily the left hemisphere plays an important role in the compensation of language function. However, in fact, there are also several reports that demonstrate that the right hemisphere is involved in the compensation of language function.

Ohyama et al. [9] demonstrated by use of PET that in patients with motor aphasia resulting from impairment of the left frontal lobe the degree of language function recovery was correlated with the degree of right frontal lobe activation. Moreover, Abo et al. [10] showed by use of functional MRI (fMRI) that in patients in whom a favorable recovery of language functions was observed also an activation of the right hemisphere was seen. Moreover, Richter et al. [11] announced similar findings in a study that used fMRI.

In view of these clinical reports, we think that there is a possibility that in case of aphasia resulting from impairment of the left frontal lobe the site that can compensate language function is not necessarily limited to the left hemisphere but that depending on the patient rather the right hemisphere plays a central role in the compensation of language functions. Therefore, high activation levels in the right hemisphere, which are seen when the left hemisphere was damaged, are not necessarily

a maladaptive response but depending on the patient can be interpreted to indicate "new activity that can be used for the compensation of language functions."

4 Application of Functional MRI in Therapeutic Approach to Aphasia

Not only when applying rTMS for the treatment of aphasia but also when applying rTMS for the treatment of other neurological sequelae of stroke, it is important that the neural activity of the site that compensates impaired functions is activated. Considering the diversity of sites that can compensate language function in patients with aphasia resulting from impairment of the left frontal lobe, it is desirable to sort out which site can compensate language function before applying rTMS treatment in patients with aphasia.

For instance, it is believed that the possibility cannot be ruled out that the compensation of language functions might become inhibited, if low-frequency rTMS is applied to a brain area that compensates language function, and that as a result language functions aggravate. At present, however, there are no special clinical findings that suggest sites that compensate language function in patients with aphasia, and it is also not possible to evaluate such sites by common head CT or MRI. Therefore, we considered that it might be possible to evaluate sites that compensate language function in patients with aphasia by use of fMRI images that were obtained while the patient performed verbal tasks and devised a therapeutic approach of rTMS, which is conducted based on such images.

It is a treatment concept in which sites that showed activity on fMRI images that were obtained while the patient performed verbal tasks are considered compensatory sites of language function and in which the compensation of language function is promoted by reducing the interhemispheric inhibition of the activated site by applying low-frequency rTMS to the contralateral hemisphere [12]. In short, for motor aphasia resulting from impairment of the left frontal lobe, in patients with activity in the left hemisphere on fMRI images that were obtained while the patient performed verbal tasks, low-frequency rTMS is applied to the inferior frontal gyrus of the right frontal lobe, and in contrast, in patients with activity in the right hemisphere on fMRI images that were obtained while the patient performed verbal tasks, low-frequency rTMS is applied to the inferior frontal gyrus of the left frontal lobe (Fig. 3.3).

There is a notable report on this method that was also published by Naeser et al. [13] According to Naeser et al., in patients in whom fMRI imaging of verbal tasks prior to the application of rTMS confirmed activity not only in the right but also in left hemisphere, not only language functions such as naming recovered after application of low-frequency rTMS to the right frontal lobe, but also increased activation of the left hemisphere was confirmed on fMRI images. On the other hand, in patients in whom fMRI images prior to the application of rTMS only confirmed activity in the right hemisphere, through the application of low-frequency rTMS to the right

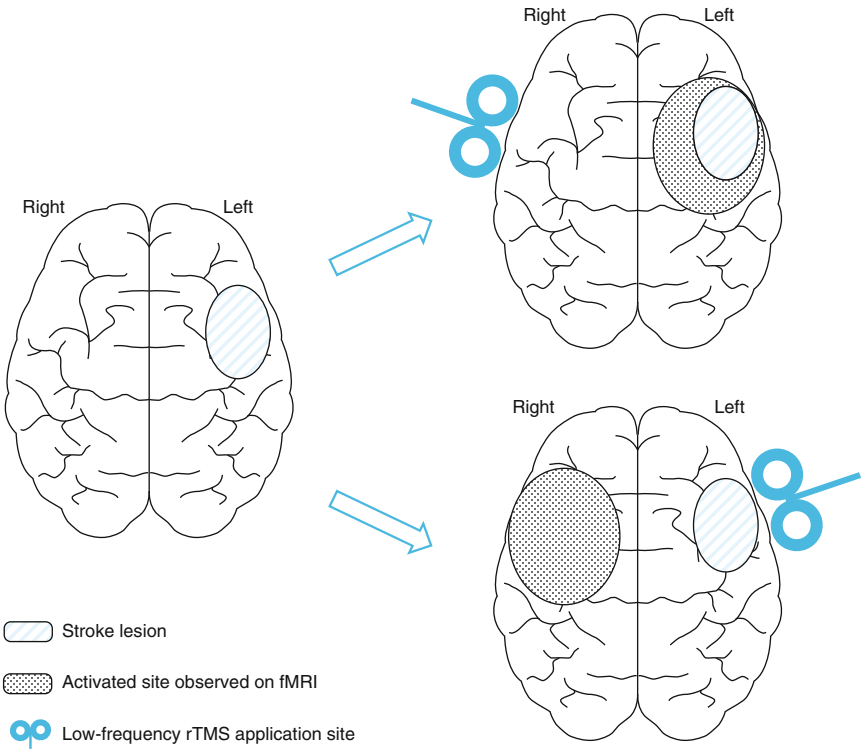

Fig. 3.3 Application site for low-frequency rTMS determined based on fMRI findings. Low-frequency rTMS is applied over the hemisphere contralateral to the activated site on fMRI images

frontal lobe neither a recovery of language functions nor increased activity was observed at any site. Therefore Naeser et al. concluded that "it is unlikely to achieve positive effects through the application of low-frequency rTMS to the right hemisphere in patients in whom no activity was observed in the left hemisphere on fMRI images taken prior to the application of rTMS," and we think that this supports our concept."

5 Protocol of Low-Frequency rTMS in Combination with Intensive Speech and Language Therapy

In a cooperative study with the Division of Radiological Science, Faculty of Health Science, Tokyo Metropolitan University, which has excellent expertise in fMRI imaging, we conduct rTMS for the treatment of poststroke aphasia resulting from lesions in the left frontal lobe since 2007. This therapy is only conducted in those patients who visited our outpatient department (Department of Rehabilitation, Jikei

University Hospital) because they wish to undergo this treatment and who fulfill the eligibility criteria. Our treatment policy is to determine the site that is suitable for treatment, based on the results of fMRI images that were obtained while the patient performed verbal tasks, and then to perform low-frequency rTMS in combination with intensive ST on consecutive days after the patient was hospitalized at our department (Fig. 3.4). The actual protocol is described below.

A. Eligibility Criteria

The current eligibility criteria are the same as those listed in Table 3.1, such as the contraindications for rTMS in the guidelines suggested by Wassermann [14]. However, these criteria are considered to be only provisional, and it should be noted that these criteria might be revised in the future.

B. fMRI Images of Verbal Tasks

For the evaluation of compensatory sites of language function, fMRI images that are obtained while the patient is performing verbal tasks are taken at least 4 weeks prior to hospitalization for undergoing rTMS treatment.

All MRI images are obtained by use of 3.0-Tesla equipment, which enables echo-planar imaging. fMRI is performed using gradient-echo echo-planar imaging, and imaging parameters are set as follows: slice thickness 5 mm, field of view (FOV) 230 mm, time of repetition (TR) 5000 ms, time to echo (TE) 35 ms, flip angle 90°, and matrix size 128 × 128.

One fMRI examination session is performed under two conditions, namely, in performing speech repetition tasks and in a resting state. Speech repetition task is to repeat aloud the short words that can be heard every 5 minutes via earphone. However, before performing speech repetition tasks, we confirmed whether the

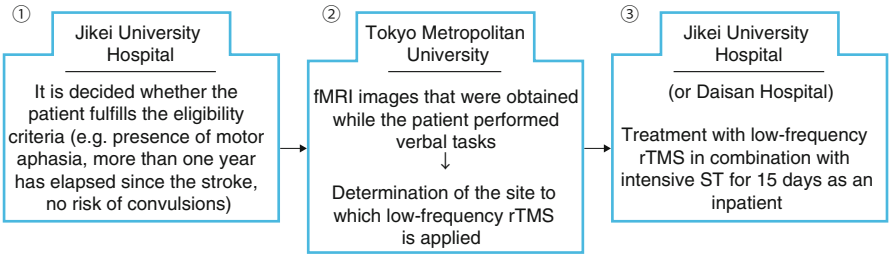

Fig. 3.4 Procedure of the application of rTMS for the treatment of aphasia at our department. In patients who fulfill the eligibility criteria, fMRI is conducted while the patient performs verbal tasks, and the site to which low-frequency rTMS is applied is determined

Table 3.1 Eligibility criteria for the applications of rTMS for the treatment of aphasia

1.	Presenting mild-to-moderate motor aphasia due to stroke (e.g., ability, at least, to speak short sentences comprising two to four Japanese words, to repeat aloud nouns frequently used in daily living settings, to understand and follow simple verbal commands, to communicate with others in daily living settings)
2.	Age at application of treatment between 18 and 80 years
3.	The latency between the onset of stroke and application of treatment is more than 12 months
4.	History of a single stroke only (no bilateral cerebrovascular lesion)
5.	No apparent cognitive impairment (other than aphasia)
6.	No apparent changes in language function at least three months prior to the application of treatment (despite of speech rehabilitation)
7.	No active systemic physical or mental illness requiring medical management
8.	No pathological conditions known to be contraindications for rTMS in the guide-lines suggested by Wassermann (e.g., intracranial metals, cardiac pacemaker, pregnancy)
9.	No recent history of seizure (documented epileptic discharge on recent electroencephalography or current use of antiepileptic medications for the prevention of seizure)

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patient who was examined was able to repeat correctly most of the words that he or she heard.

Moreover, simultaneously, for the accurate positioning of the activated site that was superimposed on fMRI images, also horizontal and coronal T1-weighted images were taken. The imaging parameters for T1-weighted images were set as follows: slice thickness 2 mm, FOV 240 mm, TR 26 ms, TE 2.4 ms, flip angle 80°, and matrix size 256×256. fMRI images were analyzed by use of statistical parametric mapping 2 (SPM2) software implemented in MATLAB® for the analysis of brain imaging data. Analyzed images were displayed in such a way that they were superimposed on horizontal and coronal T1-weighted images. Sites with an increase in local blood flow (*P* values of 0.01 or less) were shown as significant activated site, and the *T* value (indicates the degree of increase in blood flow) of each activated site was automatically calculated. Furthermore, the hemisphere that contained the activated site with the highest *T* value was considered to be the "compensatory language function hemisphere."

Figure 3.5 represents typical examples of fMRIs in which activation is seen in the left and right hemisphere, respectively.

C. Application of Low-Frequency rTMS

Low-frequency rTMS stimulation of 1 Hz is performed by use of MagPro R30 and a figure-8 coil (both manufactured by MagVenture). One session lasts 20 minutes, and thus during one session 1, 200 pulses of 1 Hz are applied. At first we decided to

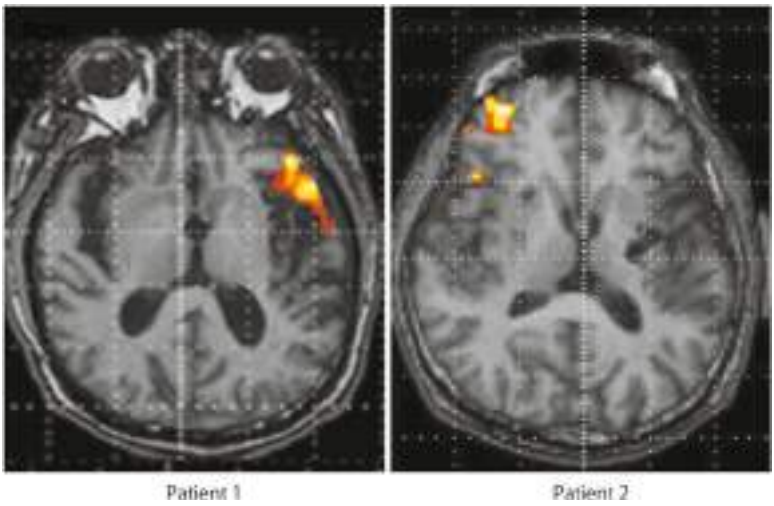

Fig. 3.5 fMRI images that were obtained while the patient performed verbal tasks. Activation can be seen in the left frontal lobe for patient 1 and in the right frontal lobe for patient 2

set the site contralateral to "the site that showed the strongest activation on fMRI" as stimulation site; however, it was extremely complicated to work out a method pursuant to this idea (MRI images were taken after marking the site, e.g., with a coin, and the stimulation site was determined by correcting deviations between the target site and the position of the coin). Moreover, some voiced the opinion that "if it were possible to accurately determine to which hemisphere rTMS should be applied, then it would not be necessary to stimulate the site exactly contralateral to the maximum activated site."

Therefore, at present the inferior frontal gyrus of the frontal lobe in the hemisphere contralateral to "the hemisphere that contains the most activated site on fMRIs" is set as the stimulation site (in the left hemisphere this corresponds to the Broca's area, and in the right hemisphere this corresponds to the region contralateral to the Broca's area). Furthermore, for determining the position of the inferior frontal gyrus of the frontal lobe we apply the International 10–20 system.

Previously, Homan et al. [15] and Okamoto et al. [16] examined in detail the correlation between International 10–20 system electrode placement sites and cerebral localization. As a result, both research groups concluded that the F7 region (left hemisphere) and F8 region (right hemisphere) correspond to the inferior frontal gyrus of the frontal lobe. Therefore, in patients in whom activation was observed in the left hemisphere on fMRI we use the F8 region as stimulation site, and in patients in whom activation was observed in the right hemisphere on fMRI we use the F7 region as stimulation site (Fig. 3.6).

MagPro R30 is equipped with an arm with which the stimulation coil is fixated, and because this arm is very strong, as long as the patient does not move markedly,

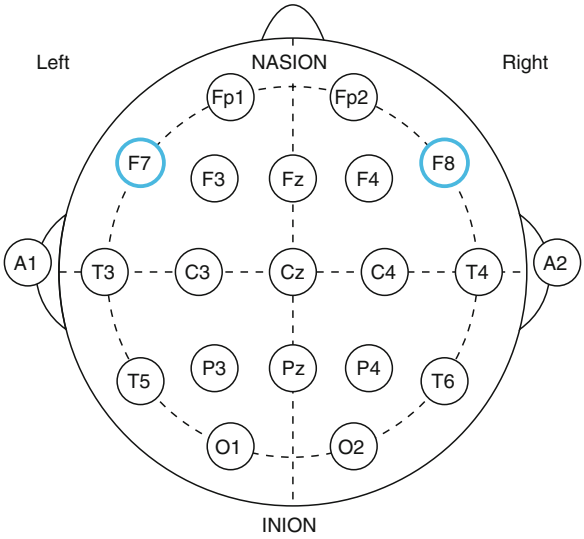

Fig. 3.6 F7 and F8 regions of the International 10–20 system. The F7 and F8 regions correspond to the inferior frontal gyrus of the frontal lobe

it will rarely happen that the stimulation site will be misaligned. However, during rTMS the physician should always stay by the patient, and frequently check whether the stimulation site has become misaligned, and also watch out for adverse events or adverse reactions. We thought to put a small circular sticker on the stimulation site once it was determined, or to mark the stimulation site on the skin by use of a marker pen (p. 124), so that at the next treatment session rTMS could be applied to the same site. Regardless to which hemisphere rTMS is applied, intensity was set at 90 % of the minimum intensity (motor threshold) measured with which MEP can be induced in the left (nonparalyzed side) thenar muscles of upper limb (Table 3.2).

D. Treatment Protocol During Hospitalization

rTMS treatment for the treatment of aphasia is performed in combination with intensive ST and requires hospitalization for a period of 15 days (Table 3.3). In principle, except for the day of hospitalization/discharge and Sundays, every day twice low-frequency rTMS is performed for 20 minutes, and twice intensive ST is performed for 60 minutes. Intensive ST is a one-on-one training with a speech therapist that is individually designed according to the severity and impaired functions of the patient, but essentially this program focuses on the strengthening of speech modalities.

This program mainly comprises, for instance, “training by use of sentences to describe the contents” about presented pictures or cartoons, “training to repeat aloud” the words or sentences the therapist said, and “training to dictate” as listening to short words or sentences. Language functions were assessed at least twice, namely, prior to hospitalization and at time of discharge, by use of the standard

Table 3.2 An example of rTMS treatment for the treatment of aphasia[a]

Coil used	Figure-8 coil
Site	Non-lesional hemisphere (frontal lobe inferior frontal gyrus)
Intensity	90 % of motor threshold
Frequency	Low-frequency rTMS (1 Hz)
Duration	1 session lasting 20 minutes (1200 pulses), once or twice daily
No. of days of hospitalization	15 days

[a]The actual therapeutic regimen is adjusted by each institution

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language test of aphasia (SLTA) and the Japanese version of western aphasia battery (WAB). In the "Japanese Guidelines for the Management of Stroke 2009" [2] the use of SLTA as well as the Japanese version of WAB is recommended with Grade B evidence.

E. Results

Here, we introduce the results from the pilot study of this combination treatment in 12 patients with motor aphasia resulting from left frontal lobe stroke conducted between 2009 and 2011 [17].

This study included six patients each with intracerebral hemorrhage of the left putamen and with left middle cerebral artery infarction. Mean age at the time of treatment was approximately 55 years old, and approximately 38 months had passed between stroke onset and intervention. fMRI images that were obtained while the patient performed verbal tasks revealed the left hemisphere was activated in nine patients and the right hemisphere in three patients. Therefore, in nine patients low-frequency rTMS was applied to the F8 region, and in three patients low-frequency rTMS was applied to the F7 region (Table 3.4) [17]. As described above, each patient was hospitalized for 15 days and during this period underwent the treatment with 20 minutes of low-frequency rTMS in combination with 60 minutes of ST twice daily.

As a result, we found that the rate of correct answers obtained when testing naming in the SLTA test or repetition in the WAB test had significantly improved. Moreover, also a tendency of improved correct answer rates for other items (speech repetition and handwriting in the SLTA test) was observed (Table 3.5) [17]. Based on these results, we speculated that the application of low-frequency rTMS had increased the plasticity of compensatory sites of language function shown on fMRI and that in combination with intensive ST the functional reconstruction of language functions had been promoted, and we considered that it would be useful to check this over time (before and after treatment) by functional brain imaging such as fMRI or PET. In addition, we think that the results of this study confirmed the safety of this combination treatment; however, there is a possibility that the duration

Table 3.3 Example of the hospitalization of rTMS treatment for the treatment of aphasia[a]

	Thur	Fri	Sat	Sun	Mon to Sat	Sun	Mon and Tues	Wed	Thur
Morning	Admission	Evaluation at admission	Low-frequency rTMS (20 minutes)	No treatment	Low-frequency rTMS (20 minutes)	No treatment	Low-frequency rTMS (20 minutes)		Discharge
			One-to-one training (60 minutes)		One-to-one training (60 minutes)		One-to-one training (60 minutes)		
Afternoon	Pre-treatment evaluation	Low-frequency rTMS (20 minutes)			Low-frequency rTMS (20 minutes)		Low-frequency rTMS (20 minutes)	Post-treatment evaluation	
		One-to-one training (60 minutes)			One-to-one training (60 minutes)		One-to-one training (60 minutes)		

[a]An example of being hospitalized on Thursday
The actual hospitalization schedule is adjusted by each institution
As of December, 2012

Table 3.4 Clinical characteristics of studied patients

No	Gender	Age at intervention (years)	Time between stroke onset and intervention (m)	Type of stroke	Site of lesion	Hemisphere including the most activated area	rTMS application site
1	M	49	31	Intracerebral hemorrhage	Left putamen	Left	F8
2	M	58	27	Intracerebral hemorrhage	Left putamen	Left	F8
3	M	57	51	Cerebral infarction	Left middle cerebral artery territory	Left	F8
4	M	61	15	Cerebral infarction	Left middle cerebral artery territory	Left	F8
5	F	56	30	Cerebral infarction	Left middle cerebral artery territory	Left	F8
6	M	49	41	Cerebral infarction	Left middle cerebral artery territory	Left	F8
7	M	59	33	Intracerebral hemorrhage	Left putamen	Left	F8
8	M	46	19	Cerebral infarction	Left middle cerebral artery territory	Left	F8
9	F	44	28	Intracerebral hemorrhage	Left putamen	Left	F8
10	M	58	15	Intracerebral hemorrhage	Left putamen	Right	F7
11	M	66	115	Intracerebral hemorrhage	Left putamen	Right	F7
12	M	62	48	Cerebral infarction	Left middle cerebral artery territory	Right	F7

Reference [17]

Table 3.5 Changes in outcome measures by intervention

Outcome measures		Correct answer rate (%)		*P* value
		Pre-intervention	Post-intervention	
SLTA	Naming	77.5 ± 18.3	84.6 ± 15.3	<0.05
	Repetition	75.1 ± 17.9	78.4 ± 15.0	0.082
	Writing	70.4 ± 34.6	73.3 ± 30.1	0.22
Japanese version of WAB	Repetition	68.7 ± 27.0	75.7 ± 25.9	<0.05

Reference [17]

of intervention (duration of hospitalization) or the duration of rTMS were not optimal, and therefore these points require further examination.

6 Future Challenges

To this point, we have described the therapeutic application of rTMS for the treatment of poststroke motor aphasia; however, until now there are almost no reports on the therapeutic application of rTMS for the treatment of sensory aphasia.

As described above, motor aphasia typically results from impairment of the frontal lobe, and sensory aphasia results from impairment of the temporal lobe. There are attempts also to treat patients with sensory aphasia who have lesions in the temporal lobe by applying rTMS to the frontal lobe, similar to the treatment of motor aphasia; however, we remain dubious as to whether this is appropriate. In fact, the neural connections between both hemispheres do not only correspond one to one, and therefore it is expected that there is also a possibility that the application of rTMS to the frontal lobe may affect the contralateral temporal lobe; however, the impact thereof might not be sufficient.

Therefore, we thought that for the treatment of sensory aphasia resulting from temporal lobe lesions, rTMS should also be applied to the temporal lobe (although there is not much evidence for this concept). We also thought that, particularly when the left hemisphere is affected, the superior temporal gyrus of the temporal lobe that corresponds to the Wernicke's area should be used as the stimulation site and actually selected CP5 (left hemisphere) and CP6 (right hemisphere), which according to the International 10–20 system correspond to the superior temporal gyrus as stimulation sites. Recently, the application of rTMS treatment is not ruled out even for the treatment of sensory aphasia, and a "therapeutic rTMS concept that does not only take into consideration of findings prior to the application of rTMS, but also of the type of aphasia" has been started. More specifically, based on fMRI findings and the type of aphasia (clinical findings) patients are divided into four groups, as shown in Fig. 3.7, and for each type rTMS application site is selected. In summary patients are divided into the following groups:

(i) For motor aphasia with activation in the left hemisphere on fMRI, low-frequency rTMS is applied to the F8 region (right hemisphere).

(ii) For motor aphasia with activation in the right hemisphere on fMRI, low-frequency rTMS is applied to the F7 region (left hemisphere).
(iii) For sensory aphasia with activation in the left hemisphere on fMRI, low-frequency rTMS is applied to the CP6 region (right hemisphere).
(iv) For sensory aphasia with activation in the right hemisphere on fMRI, low-frequency rTMS is applied to the CP5 region (left hemisphere).

The outcome of this new treatment concept so far is generally favorable [18]. Moreover, we have consistently used low-frequency rTMS for the treatment of patients with aphasia, but we believe that also approaches should be tested that use high-frequency rTMS instead. More specifically, this is a treatment concept that tries to facilitate the neural activity of compensatory sites of language function directly by applying high-frequency rTMS to compensatory sites of language function that were determined by fMRI. Eventually it will become necessary to compare the effects of approaches that use this kind of high-frequency rTMS and approaches that use low-frequency rTMS as we do on the improvement of language functions.

From the results of our initiatives we expect that similar to other neurological sequelae of stroke, the recovery of poststroke aphasia can be facilitated by performing intensive ST after the brain's plasticity was increased by use of rTMS. However,

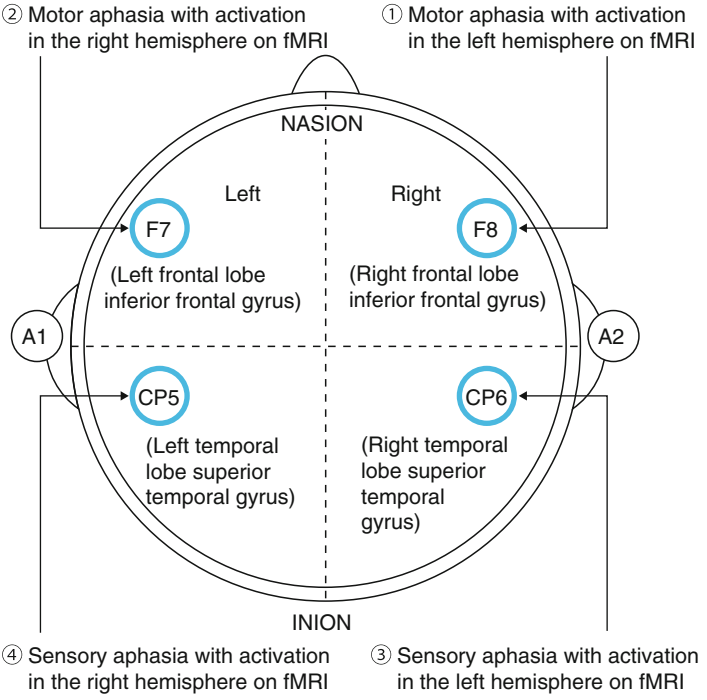

Fig. 3.7 Application site of rTMS based on fMRI findings and the type of motor aphasia, low-frequency-rTMS is applied to the frontal lobe. On the other hand, in case of sensory aphasia, low-frequency rTMS is applied to the temporal lobe

an important point with regard to the treatment of aphasia by use of rTMS is the determination of the site that can compensate language function before applying rTMS. We sincerely hope that in the future the usefulness of conservative language rehabilitation will increase through the appropriate application of rTMS treatment.

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Chapter 4
rTMS for Poststroke Dysphagia

1 Pathology and Current Status of the Treatment

A. Etiology and Pathology of Dysphagia

Besides organic disorders of the oral cavity and pharynx, dysphagia is caused by neuromuscular dysfunction, which can also be associated with aging. Furthermore, stroke-related dysphagia is frequently encountered in daily clinical practice, and apparently during the acute phase of stroke about half of patients experience dysphagia. Since dysphagia affects ADL, QOL, and prognosis of the patients with stroke, it is of primary importance to find methods on how to handle dysphagia.

At present, the central pattern generator (CPG), which is located in the brainstem, is considered to be the swallowing center. The CPG consists of the solitary nucleus and the reticular formation and receives information from both hemispheres of the cerebral cortex. Neural input from the cerebral cortex that is transmitted to the CPG is conveyed via, e.g., the trigeminal nerve nucleus, facial nucleus, ambiguous nucleus, hypoglossal nucleus, and dorsal nucleus of the vagus nerve to swallowing-related muscle groups (Fig. 4.1). The CPG also receives input from peripheral receptors that are located in the oral cavity and pharynx via cranial nerves such as the trigeminal nerve, glossopharyngeal nerve, and vagus nerve.

In recent years, it has been increasingly emphasized that the smooth control of swallowing movements is not only regulated by the brainstem but also by the cerebral cortex. Allegedly the primary motor area, sensory area, insular cortex, and cingulate gyrus are important swallowing-related areas of the cerebral cortex. In most cases of dysphagia that are caused by supratentorial lesions, these lesions occur bilaterally. However, it is known that even if supratentorial lesions occur unilaterally approximately 30 % of patients develop dysphagia, and that in most of these patients dysphagia resolves within approximately 1 month. Therefore, it is

M. Abo, W. Kakuda, *Rehabilitation with rTMS*,
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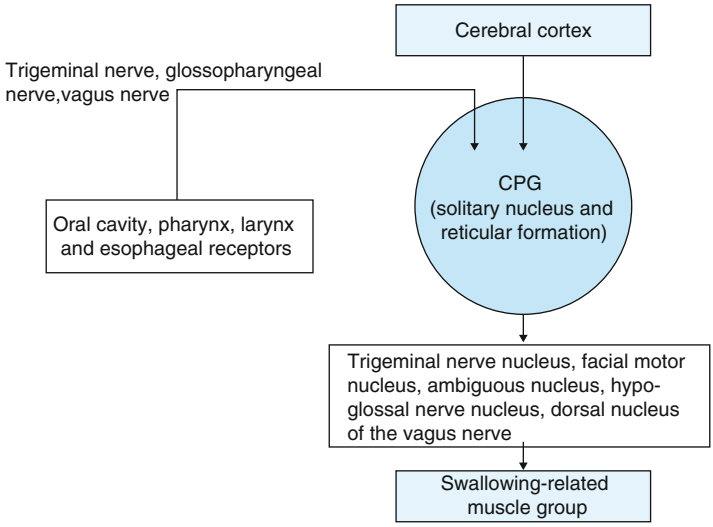

Fig. 4.1 Swallowing center. The swallowing center (CPG) is located in the brainstem. It is controlled by both hemispheres of the cortex, and also receives input from peripheral receptors

believed that in such cases the nonlesional hemisphere compensates for the affected hemisphere, and that this results in functional recovery.

It has been found that the stimulation of swallowing-related muscles by use of TMS (Fig. 4.2) results in the constriction caused by both hemispheres, which showed that swallowing-related muscles are controlled by both hemispheres. Moreover, although there are slight individual differences with respect to whether the right or left hemisphere is more dominant in terms of the control of swallowing, from our experience we have the impression that dominance of the right hemisphere is slightly more frequent. In cases where dysphagia is caused by unilateral lesions, there is a possibility that dysphagia results from damage to the originally dominant side.

B. Dysphagia Rehabilitation Methods

The following are three dysphagia rehabilitation methods that have been confirmed to be effective in comparative studies.

1) Head Raising Exercises

Head raising exercises are performed to strengthen the suprahyoid muscle group, improve movement of the hyoid bone and larynx, and reduce pharyngeal residues and aspiration [1].

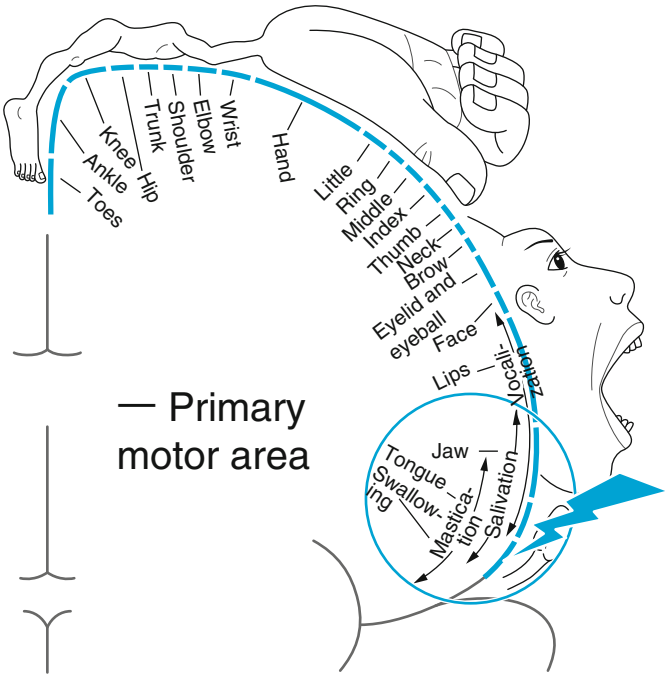

Fig. 4.2 Location of swallowing-related muscles in the primary motor cortex. As shown in Penfield's homunculus, all regions that represent swallowing-related muscles are located slightly below the lateral surface of the frontal lobe

2) McNeill Dysphagia Therapy Program

The McNeill dysphagia therapy program (MDTP) is a program in which foods of various consistency are to be swallowed for enhancing swallowing coordination. This program is characterized by combining single swallow strategies (to swallow foods or liquids in one attempt through strong swallowing) with remaining functions of the patient, and gradually food with a consistency that is increasingly difficult to swallow is given. When performing MDTP in patients with chronic dysphagia once daily for 1 hour over a period of 3 weeks, a significant improvement in findings on videofluoroscopic examination of swallowing was observed, and it was reported that this effect still was maintained 3 months later [2].

3) Electrical Stimulation of the Neck

Electrical stimulation of the neck is a method through which swallowing function is improved by electrical stimulation of the neck. This method has been reported to be useful [3], but there is no consensus on stimulation parameters and stimulation sites.

2 Idea Underlying the Application of rTMS in Combination with Dysphagia Rehabilitation

A. Previous Reports on the Application of rTMS

As of December 2012, when searching on MEDLINE the keywords "stroke, dysphagia, repetitive transcranial magnetic stimulation" we found 18 articles, and when searching the keywords "brain injury, dysphagia, repetitive transcranial magnetic stimulation" we found 5 articles. Among these were six research papers that actually examined the beneficial effects of rTMS on swallowing function in patients with poststroke dysphagia, which are shown in Table 4.1.

Khedr et al. [4] reported that swallowing function improved in the patients with supratentorial stroke when applying 3-Hz (120 %) high-frequency rTMS to the esophageal region of lesional primary motor area once daily over a period of 5 days. On the other hand, Verin et al. [5] reported that the swallowing reaction time, pharyngeal residue score, and aspiration score improved in the patients with supratentorial stroke when applying 1-Hz (120 %) low-frequency rTMS once daily for 20 minutes over a period of 5 days to the region of the nonlesional primary motor area that represents the laryngeal elevator muscle group. Moreover, Kim et al. [6] reported that when treating supratentorial stroke patients within 3 months after onset, the dysphagia scale as well as aspiration and laryngeal penetration improved more by low-frequency rTMS to the nonlesional hemisphere than by high-frequency rTMS to the lesional hemisphere. Besides, Michou et al. [7] reported that pharyngeal transit time, aspiration, and laryngeal penetration improved after performing paired-associative stimulation (PAS) by peripheral electrical stimulation and rTMS to the nonlesional primary motor area of patients with poststroke dysphagia. Furthermore, Park et al. [8] reported that in a double-blind RCT the dysphagia scale, aspiration, and laryngeal penetration significantly improved when applying 5-Hz (90 %) rTMS once daily for 20 minutes over a period of 2 weeks to the nonlesional pharyngeal motor area.

These reports are mainly on interventions that were performed in patients with supratentorial lesions; however, patients who had a subtentorial stroke, e.g., in the brainstem are actually those who suffer the most from dysphagia. Khedr et al. [9] reported that in patients with subtentorial stroke involving the brainstem and medulla oblongata, etc. the dysphagia scale significantly improved compared to the sham stimulation group (factitious stimulation) when performing 3-Hz (130 %) high-frequency stimulation once daily for 5 days to the esophageal region of primary motor area in both hemispheres (Fig. 4.3).

In a report on stimulation frequency and plasticity [10], MEP obtained after stimulation of the pharyngeal motor area at 1 Hz, 5 Hz, and 10 Hz were compared, and it was found that the largest MEPs were obtained after stimulation at 5 Hz (Fig. 4.4). Moreover, there is a report in which alterations in the MEPs of pharynx muscles were measured when applying rTMS not only to the cerebrum but also to the cerebellum [11], Based on these results it was considered that the cerebellum is involved in the regulation of swallowing process, and it was suggested that rTMS of the cerebellum might have an impact

Table 4.1 Research papers that examined the beneficial effects of rTMS on swallowing function

Name of author	Number of patients	Time from stroke onset	Stimulation sites	Stimulation methods	Clinical effects
Khedr EM, et al. (Acta Neurol Scand 2009)	26 stroke (unilateral cerebral lesion)	5–10 days	Lesional primary motor area	3 Hz (120 %)	Improved dysphagia score
Verin E, et al. (Dysphagia 2009)	7 stroke (2 cerebellar lesion)	11–132 months	Non-lesional primary motor area	1 Hz (120 %)	Improved swallowing response time, pharyngeal residue and aspiration score
Khedr EM, et al. (J Neurol Neurosurg Psychiatry 2010)	22 brainstem or medullary infarction	Within 3 months	Both primary motor cortices	3 Hz (130 %)	Improved grade of dysphagia
Kim L, et al. (Ann Rehabil Med 2011)	2 brain injury, 28 stroke (unilateral cerebral lesion)	Within 3 months	Lesional or non-lesional primary motor area	1 Hz or 5 Hz 100 %	Improved dysphagia scale, aspiration and laryngeal penetration at 1 Hz
Michou E, et al. (Gastroenterology 2012)	6 stroke (unilateral cerebral lesion)	6 months or longer (mean 38.8 weeks)	Non-lesional primary motor area	PAS	Improved pharynx transit time, aspiration and laryngeal penetration
Park JW, et al. (Neurogastroenterol Motil 2012)	18 stroke (unilateral cerebral lesion)	1–3 months	Non-lesional primary motor area x	5 Hz (90 %)	Improved dysphagia scale, aspiration and laryngeal penetration

on swallowing function. Moreover, in each study different methods were used for determining the stimulation site. In previous reports on rTMS for the treatment of dysphagia, the stimulation site was mostly determined by measuring MEP of the laryngeal elevator muscle group by use of a surface electromyogram of the neck or by measuring MEP of the laryngopharynx and esophagus by use of catheter electrodes (Fig. 4.5).

Even though all these treatment methods are termed rTMS for the treatment of poststroke dysphagia, as shown in Table 4.1, there exist various stimulation modalities, and also the stimulation method that we use at our facility is the result of continuous trial and error. At first, we were primarily concerned about the safety of the

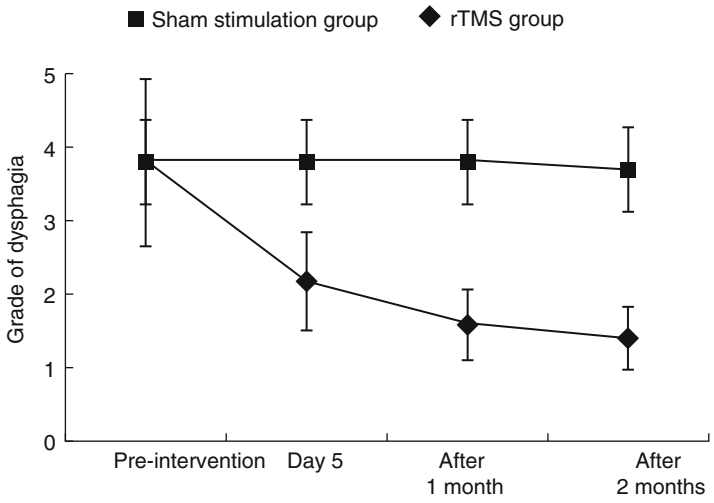

Fig. 4.3 Efficacy of bilateral magnetic stimulation. The dysphagia scale improved significantly more in the rTMS (3 Hz) group than in the sham stimulation group [7]

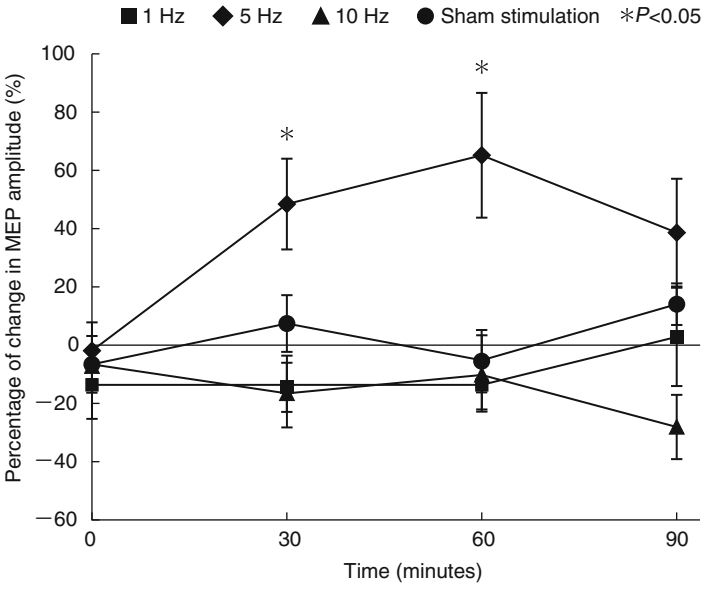

Fig. 4.4 Percentage of change in MEP amplitude by frequency. The greatest percentage of change in MEP amplitude (%) was obtained after stimulation at 5 Hz (Adapted from Ref. [10])

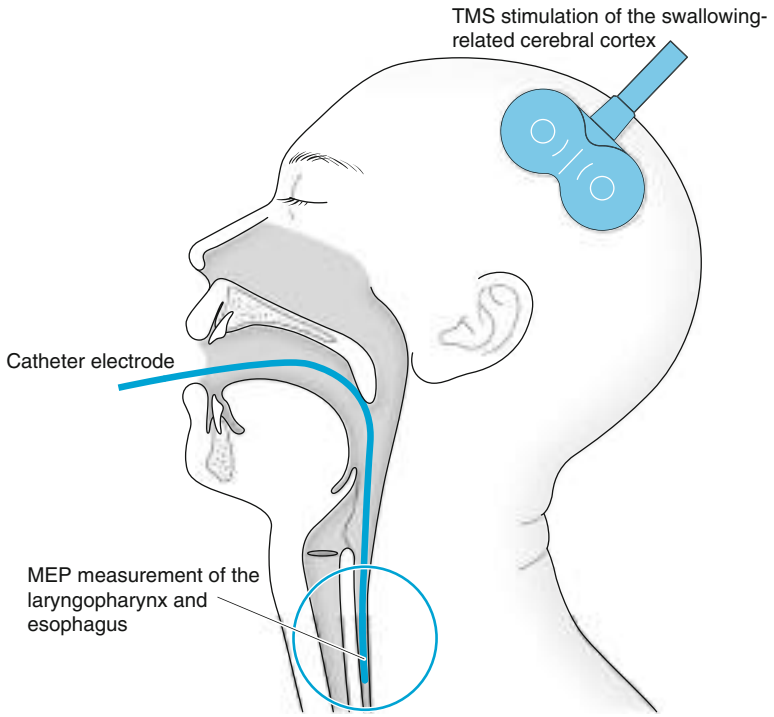

Fig. 4.5 Determination of the stimulation site by use of catheter electrodes. By use of a catheter that is inserted orally, MEPs of the laryngopharynx and esophagus are measured to determine the application sites of rTMS

patient and performed stimulation of the nonlesional hemisphere at 1 Hz. However, since there is only little lateralization in swallowing function because it is controlled by both hemispheres, and long-term dysphagia resulting from unilateral lesions is rare, at present we mostly use a bilateral rTMS (3–5 Hz) treatment protocol.

As described in the report in which bilateral stimulation was performed, the biggest advantage of this method is that one does not have to give too much thought to right or left laterality, and thus does not have to be concerned about the site of the lesion. Moreover, for increasing the plasticity of the pharyngeal region of primary motor area, we determine the stimulation site by measuring the MEP of pharyngeal muscles by use of catheter electrodes.

B. Eligibility Criteria for rTMS Treatment

Below are shown the eligibility criteria of rTMS for the treatment of poststroke dysphagia that are used at our hospital; however, they are only provisional (Table 4.2). Criterion 2 refers to patients in whom the use of rTMS is

Table 4.2 Eligibility criteria for rTMS for the treatment of poststroke dysphagia

1.	Presents with dysphagia caused by stroke (cerebral infarction, brain hemorrhage, or subarachnoid hemorrhage)
2.	No intracranial metal objects (e.g. a clip), or implanted cardiac pacemaker
3.	No recent history of convulsions at least within one year preceding the intervention (no abnormalities on electroencephalographic examination)
4.	No patient with severe dysphagia who constantly aspires saliva
5.	No patient with mild dysphagia, in whom the oral intake of a regular diet is possible
6.	Favorable general condition (no severe complications such as impaired consciousness, fever, or severe cardiac disease)
7.	Is not on dialysis
8.	No mental illness such as depression
9.	Underwent no tracheotomy, does not require aspiration, and also good respiratory status
10.	No recent history of pneumonia within three months preceding the intervention
11.	Can remain in a seated position for at least two hours, and does not require much assistance for daily living
12.	No significant cognitive impairment
13.	Is willing to undergo rehabilitation
14.	The age between 20 and 80 years

As of December, 2012

contraindicated, and criterion 3 was set up for excluding patients with epilepsy. Criterion 4 and 5 were set up for excluding patients with very severe or mild dysphagia, because from our experience in these patients rTMS is not very effective. Criteria 6 to 13 were set up for ensuring that the patient is in a condition that enables to perform intensive rehabilitation. Moreover, considering the patient's ability to give consent, we set up an age limit as can be seen in criterion 14 (we are planning to extend this age limit in the future).

C. Performing rTMS in Combination with Intensive Dysphagia Rehabilitation

Since the effects obtained by rTMS alone usually only last for a short period, long-term improvement requires dysphagia rehabilitation. Therefore, the patient is hospitalized for 1 to 2 weeks for performing rTMS and intensive dysphagia rehabilitation. Our treatment protocol is designed for rTMS that focuses on the pharyngeal phase of dysphagia, and therefore we consider it useful to combine this treatment with dysphagia rehabilitation for the pharyngeal phase of dysphagia. Specifically, we think that, e.g., the exercise for elevating the dorsum of the tongue, the tongue-hold-swallow exercise, mouth opening exercise [12], head raising exercise, effortful swallowing exercise (Table 4.3), and MDTP may be useful.

Table 4.3 Dysphagia rehabilitation in combination with rTMS treatment

Dorsum of tongue raising exercise	The dorsum of the tongue is depressed e.g. with a tongue depressor, and the patient is asked to resist the applied pressure by lifting his tongue, and to hold this position for a few seconds. This exercise is expected to enhance pharyngeal pressure
Tongue-hold-swallow exercise	The patient is asked to project the tongue tip forward, and to swallow saliva while keeping the tongue on his front teeth. This exercise is expected to enhance pharyngeal contraction force
Mouth opening exercise	The patient is asked to open his/her mouth as wide as possible and to hold this position for a few seconds. Then this exercise is repeated several times. This exercise is expected to increase the dilation rate of the esophageal orifice, and to improve the pharyngeal transit time
Head raising exercise	The patient is in a supine position and raises only his/her head until he/she can see his/her toe. The duration and repetition of this movement are adjusted as appropriate. Promotes bolus transit into the esophageal entrance, and reduces pharyngeal residues
Effortful swallowing exercise	The patients is asked to swallow as if squeezing something by putting force into the swallowing muscle group while pressing the tongue against the palate. Strengthens backward movement of the tongue root, and reduces pharyngeal residues

3 Protocol of rTMS in Combination with Intensive Dysphagia Rehabilitation

A. Treatment Overview

The hospitalization schedule for rTMS for the treatment of poststroke dysphagia at our department is shown in Table 4.4. In detail rTMS is applied twice daily in the morning and evening (except for the day of hospitalization/discharge and Sundays) to the pharyngeal motor cortex in both hemispheres for 10 seconds alternatively to the left and right hemisphere at 3–5 Hz (90–130 %), followed by a rest of 20 seconds, and this cycle is repeated 20 times (in total 10 minutes) (Table 4.5). Hereafter, indirect-swallowing exercises are performed for 20 minutes under the guidance of a speech therapist. Moreover, patients who are able to conduct self-exercise do additional indirect-swallowing exercises by themselves.

Usually patients are hospitalized for 6 days; they are admitted on Monday and discharged on Saturday. rTMS is conducted for 6 consecutive days, except on Sundays, and if the length of hospitalization is not limited it can be extended up to 15 days. Moreover, at the time of admission stimulation site and the intensity of stimulation are determined, and swallowing function is evaluated, and at the time of discharge swallowing function is re-evaluated.

By use of a catheter electrode (we mostly use catheter electrodes from Gaeltec Ltd.) the site at which the largest MEPs are elicited in pharyngeal muscles is

Table 4.4 An example of the hospitalization schedule used when performing rTMS for the treatment of dysphagia[a]

	Mon	Tue to Fri	Sat
Morning	Evaluation at admission	rTMS (10 minutes)	
		Dysphagia rehabilitation (20 minutes)	
Afternoon	rTMS (10 minutes)		Evaluation at discharge
	Dysphagia rehabilitation (20 minutes)		

[a]If hospitalized on Monday
As of December, 2012

Table 4.5 An example of rTMS performed for the treatment of dysphagia

Coil used	Figure-8 coil
Stimulation site	Both hemispheres (pharyngeal region of primary motor area)
Intensity	90–130 % of motor threshold
Frequency	3–5 Hz
Duration	1 session lasting 10 minutes, once or twice daily
Number of days of hospitalization	Usually 6 days (maximum 15 days)

As of December, 2012

determined and set as stimulation site on the cerebrum. First, in the imaging room of our department, MEPs are measured after having confirmed the position of the catheter electrodes on the pharynx (Fig. 4.6). Determination of the stimulation site when using catheter electrodes is a reliable method; however, it is quite cumbersome and complicated. Therefore in difficult cases, it is also possible to measure instead the MEPs that are elicited in the suprahyoid muscle group, which is also easier. For measuring the MEPs that are elicited in the suprahyoid muscle group, the electrodes should be placed between the hyoid bone and the mentum (Fig. 4.7). Besides, it is also conceivable that the stimulation site can be determined by visually confirming the movement of pharyngeal muscles resulting from TMS by videoendoscopic examination of swallowing.

B. Evaluation of Swallowing Function

At our department, before and after performing rTMS change in swallowing function is evaluated by use of a highly reliable evaluation method such as those described below.

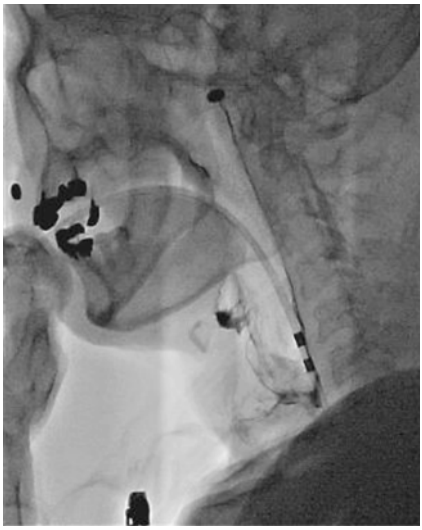

Fig. 4.6 Example showing the insertion of a catheter electrode. At our department the position of the catheter is checked by imaging

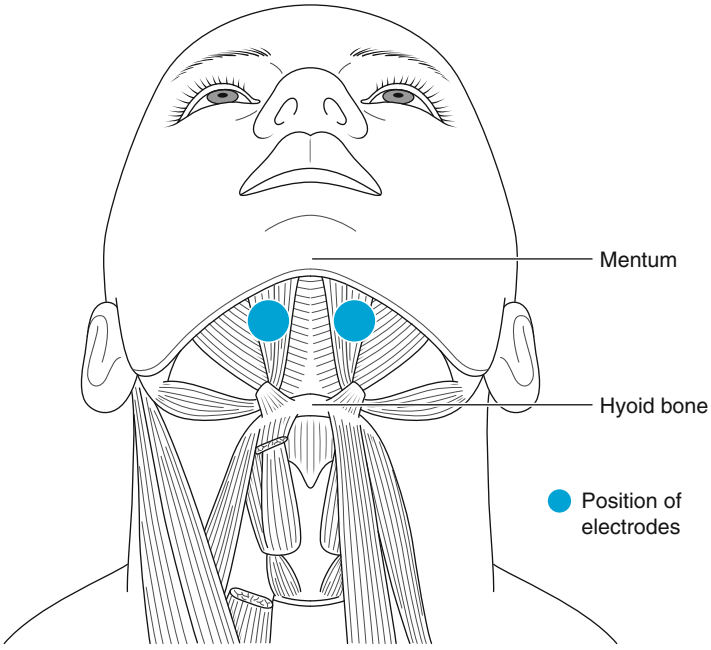

Fig. 4.7 Laryngeal elevator muscle group and position of electrodes. The stimulation site can also be determined by placing an electrode between the hyoid bone and the mentum

1) Repetitive Saliva Swallowing Test

There are some reports on that the number of voluntary swallowing increased by rTMS for the treatment of dysphagia. With the repetitive saliva swallowing test (RSST) [13], the number of times that the patient is able to swallow saliva within 30 seconds is checked, and the number of times that the patient is able to swallow saliva within 60 seconds is recorded in combination with inspection, palpation, and auscultation.

2) Mann Assessment of Swallowing Ability (MASA)

This test is widely used worldwide. It consists of 24 examination items and a 200-point grading scale, and is used for the quantitative assessment of the severity of poststroke dysphagia. The higher the score, the better are the swallowing functions of the patient. This test is also used, for instance, for the assessment of quantitative effect in the studies of interventions for dysphagia. Also its revised version, MMASA [14], which consists of 12 examination items and a 100-point grading scale, has been reported to be reliable and valid for assessing poststroke dysphagia.

3) Functional Oral Intake Scale (FOIS)

With this scale the actual oral intake of the patient is assessed based on seven levels [15]. The more difficult the food or liquid items the patient is able to take in orally, the higher the score. Moreover, another scale that is similar to the FOIS scale is the food intake LEVEL scale (FILS) [16]. FILS is frequently used in Japan and is made up of 10 levels of oral intake ability.

4) Clinical Dysphagia Scale (CDS)

This is a 100-point grading scale that is made up of 8 examination items, namely, site of lesion, tracheotomy, aspiration, lip sealing, chewing and mastication, tongue protrusion, laryngeal elevation, and reflex coughing. The higher the score, the more severe the degree of dysphagia (Table 4.6) [17].

5) Videofluoroscopic Dysphagia Scale (VDS)

This is a 100-point grading scale that is made up of 14 examination items based on which findings on videofluoroscopy of swallowing are evaluated, and it has been reported to be used, e.g., for poststroke dysphagia prognosis prediction (Table 4.7) [18]. This scale is also frequently used for assessing the effect in studies on intervention for dysphagia.

Table 4.6 Clinical dysphagia scale (CDS)

Outcome measures		Scores	Outcome measures		Scores
Location	Non-stem lesion	0	Tongue protrusion	Intact	0
	Stem lesion	5		Inadequate	4
Tracheotomy	No	0		None	8
	Yes	25	Laryngeal elevation	Intact	0
Aspiration	No	0		Inadequate	5
	Yes	10		None	10
Lip sealing	Intact	0	Reflex coughing	No	0
	Inadequate	2		Yes	30
	None	4			
Chewing and mastification	Intact	0			
	Inadequate	4			
	None	8	Total		/100

Reference [17]

Table 4.7 Videofluoroscopic dysphagia scale (VDS)

Outcome measures		Score	Outcome measures		Score
Lip closure	Intact	0	Triggering of pharyngeal swallow	Normal	0
	Inadequate	2		Delayed	4.5
	None	4	Vallecular residue	None	0
Bolus formation	Intact	0		<10 %	2
	Inadequate	3		10–50 %	4
	None	6		>50 %	6
Mastification	Intact	0	Laryngeal elevation	Normal	0
	Inadequate	4		Impaired	0
	None	8	Pyriform sinus residue	None	0
Apraxia	None	0		<10 %	4.5
	Mild	1.5		10–50 %	9
	Moderate	3		>50 %	13.5
	Severe	4.5	Coating of the pharyngeal wall	No	0
Tongue-to-palate contact	Intact	0		Yes	9
	Inadequate	5	Pharynx transit time	≦1.0 s	0
	None	10		>1.0 s	6
Premature bolus loss	None	0	Aspiration	None	0
	<19 %	1.5		Supraglottic penetration	6
	10–50 %	3			
	>50 %	4.5		Subglottic penetration	12
Oral transit time	≦1.5 s	0			
	>1.5 s	3	Total		/100

Reference [18]

6) Penetration-Aspiration Scale (P-A Scale)

This is an 8-point grading scale with which the severity of laryngeal penetration and aspiration can be assessed, and it is generally evaluated by using videofluoroscopy of swallowing [19]. The higher the score, the more severe the degree of laryngeal penetration and aspiration.

7) Laryngeal Elevation Delay Time (LEDT)

This is a swallowing examination that is performed by use of contrast material, and the results are expressed as the laryngeal elevation delay time at which maximum laryngeal elevation occurs after the contrast material reaches the esophageal entrance. It has been reported that with this method the LEDT can easily be quantitatively determined and that effects on the site of cerebral infarction are reflected with high sensitivity [20].

8) Swallowing Quality of Life (SWAL-QOL)

This is a rating scale using a dysphagia-specific self-completed QOL questionnaire, in which 44 questions on 11 areas related to swallowing are to be answered in 4–6 grades and then are assessed by a rating scale [21]. The results of each subscale are scored using a 100-point grading scale, and then expressed in a multidimensional profile. The higher the score, the higher the QOL (Table 4.8) [22]. A Japanese version has also been developed that is used together with SWAL-CARE, which is a questionnaire on the patient's satisfaction with the explanations he or she was provided regarding feeding methods and treatment and the patient's satisfaction with the medical staff [22].

4 Treatment Outcomes in Our Department

In this section we present the outcomes of rTMS for the treatment of poststroke dysphagia at our department.

A. Study Patients

We treated four patients who developed dysphagia resulting from cerebral infarction, three women and one man (Table 4.9). Age at the time of intervention ranged from 56 to 80 years old, and the time to treatment initiation from the onset of cerebral infarction ranged from 6 to 37 months. The subtype and location of cerebral infarction were diagnosed within 30 days before the start of treatment by use of

MRI. Two patients were diagnosed with bilateral cerebral infarction, one with bilateral cerebellar infarction, and one with left medullar infarction. Levels of oral food intake in these patients ranged widely, namely, from level 1 to 6 out of 7, when assessed by use of the FOIS scale.

B. Method

1) Treatment Schedule

As described above, the patients were hospitalized and underwent treatment for 6 days. In the afternoon of the day of hospitalization rTMS was performed for 10 minutes, followed by 20 minutes of one-to-one dysphagia rehabilitation. Hereafter,

Table 4.8 SWAL-QOL subscale[a]

1. Burden (Burd)
2. Eating duration (Eatdur)
3. Eating desire (Eatdes)
4. Food selection (Food)
5. Communication (Com)
6. Fear (Fear)
7. Mental health (MH)
8. Social function (Social)
9. Sleep (Sleep)
10. Fatigue (Fatig)

[a]Items included in the outcome profile

Reference [22]

Table 4.9 Clinical characteristics of studied patients

No	Age at intervention (years)	Gender	Time between onset and intervention	Site of stroke lesion	NIHSS[a]	FIM[b]
Patient 1	80	Female	24 months	Both cerebral hemispheres	5	92
Patient 2	67	Male	7 months	Left medulla oblongata	4	88
Patient 3	69	Female	6 months	Both cerebral hemispheres	5	95
Patient 4	56	Female	37 months	Both cerebellar hemispheres	5	96

[a]NIHSS (national institute of health stroke scale)

[b]FIM (functional independence measure)

this double treatment session was conducted twice daily in the morning and afternoon, on consecutive days.

2) rTMS Treatment Protocol

rTMS was performed by use of MagPro R30 and a figure-8 coil (both manufactured by MagVenture). Stimulation was performed at 3 Hz for 10 seconds (1 cycle) at intervals of 30 seconds, alternatively to the left and right primary motor cortex, and this cycle was repeated 20 times. The stimulation site was set as the location where the largest MEPs were measured for the pharyngeal muscle group by use of a catheter electrode, and the stimulation intensity was set at 130 % of the resting motor threshold derived from both the right and left abductor pollicis brevis.

3) Dysphagia Rehabilitation Program

After rTMS indirect-swallowing exercises, which were a combination of tongue movements, head raising and effortful swallowing exercises were performed in one-on-one training with a speech therapist for approximately 20 minutes, twice daily.

(i) Tongue movements included exercises such as protruding out the tongue and then drawing it back, or pressing the dorsum of the tongue against a finger, and were to be performed four to five times each, only to the extent possible without causing pain.
(ii) During the head raising exercise the patients were in a supine position with their shoulders attached to the floor, and should raise only their head until they could see their toe, followed by three-time repetition of "holding this position for one minute, followed a one minute rest." If it was difficult for a patient to raise his or her head continuously for 1 minute, the duration of this exercise was set at 50 % of the maximum possible time that the patient was able to continuously raise his/her head.
(iii) For the effortful swallowing exercise, patients were asked to press their tongue as strongly as possible against the palate "if possible for 30 seconds, followed by a rest of 30 seconds," and this was repeated two to three times.

If these exercises caused pain or fatigue on the following day, exercises were adjusted to the extent that they did not cause pain or fatigue.

4) Evaluation of Swallowing Function

Swallowing function was evaluated on the day of admission and discharge by videofluoroscopy examination of swallowing. Contrast medium was to be swallowed three times, and swallowing was evaluated based on the worst scores on the P-A scale and for LEDT. Moreover, also evaluation based on MMASA, RSST, and FOIS was performed.

C. Result

This 6-day combination treatment was completed without observing, e.g., convulsions, an aggravation of neurological symptoms, or pneumonia. Endoscopic observation of the pharynx during rTMS revealed the occurrence of swallowing-like movements. As for changes in swallowing function, a tendency of improved MMASA scores and LEDT was observed. Scores on the P-A scale, RSST, and FOIS were also unchanged or showed a trend of improvement (Table 4.10), and in no patient an aggravation of dysphagia was observed. Moreover, an improvement in the ability of oral intake and a reduction in repeated choking were observed when patients were actually taking their meals.

D. Discussion

No adverse events were observed in any of the patients in whom we carried out this treatment protocol, and therefore we believe that this treatment method is safe and highly feasible. Swallowing function is thought to be controlled bilaterally, but hemispheric dominance has also been reported [23]. However, in clinical practice, it is sometimes difficult to identify which is the dominant side, and therefore methods such as bilateral rTMS, which can be performed without having to be concerned about laterality, are highly versatile. In this study, in all patients an improvement in the triggering speed to swallowing reflex was observed.

Compared with conventional rehabilitation, the methods that we used in this treatment protocol do not require the direct use of food and therefore possibly are also safe in patients who have difficulty taking in food orally. Moreover, possibly also treatment goals that we could not sufficiently investigate in this study such as improved pharyngeal contraction force, prevention of aspiration pneumonia by reducing nocturnal saliva aspiration, and depending on the stimulation site, increased tongue pressure, improved coordination of mastication, and improved gastroesophageal reflux can be achieved in the future. Furthermore, in future studies it needs to be investigated for which subtypes or severity of stroke this treatment is effective and the timing of treatment initiation from onset. We also believe that by elucidating which symptoms of dysphagia can be improved, a more appropriate rehabilitation program can be devised.

5 Future Challenges

Attempts to use rTMS for the treatment of poststroke dysphagia have just begun, and further investigation needs to be conducted in the future. We conclude this chapter by giving an overview of the main items that require further investigation.

Table 4.10 Changes in the evaluation of swallowing function resulting from treatment

Assessment method	Patient 1		Patient 2		Patient 3		Patient 4	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
MMASA[a]	87	90	43	55	78	82	73	69
P-A scale[b]	4	1	5	2	5	2	3	3
LEDT (seconds)[c]	0.12	0.08	0.52	0.08	3.96	0.12	0.36	0.12
RSST[d]	1	2	1	1	1	2	0	0
FOIS[e]	5	6	1	2	2	3	6	6

[a]MMASA (modified Mann assessment of swallowing ability)
[b]P-A scale (penetration-aspiration scale)
[c]LEDT (laryngeal elevation delay time)
[d]RSST (repetitive saliva swallowing test)
[e]FOIS (functional oral intake scale)

1) Indications

We have the impression that when treating poststroke dysphagia by use of rTMS there are both responders who benefit from treatment and nonresponders who do not. It would be helpful if it were possible to distinguish between responders and nonresponders prior to intervention; however, currently this is not possible.

2) Treatment Protocol

In the future, detailed further investigation is required with regard to the stimulation site, intensity, frequency, details on rehabilitation exercises that should be conducted in combination with rTMS, as well as on the optimal timing of rTMS application after onset of stroke. There is also a possibility that in some cases, depending on the characteristics of the patient, this stimulation method needs to be applied in a slightly different manner.

3) Long-Term Effects

The duration of the effects that are achieved by rTMS require further investigation. At present, the long-term benefits of rTMS in patients with dysphagia have yet to be studied sufficiently. However, in patients who could be followed up after discharge, the effects of rTMS appeared to have persisted.

4) Beneficial Effects

The kinds of improvements that can be achieved by use of rTMS require further investigation. We think that it is necessary to assess multiple aspects with regard to the effects of rTMS in patients with dysphagia, such as measuring swallowing pressure before and after intervention.

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Chapter 5
rTMS for Lower Limb Hemiparesis after Stroke

Whether patients with poststroke hemiparesis have a gait disturbance or not is closely related to a drop in ADL level and a deterioration in QOL.

According to Copenhagen Stroke Study [1], 50 % of patients with stroke are unable to walk independently at the time of onset, but 80 % may regain ambulatory ability through subsequent rehabilitation. Even if ambulatory ability has been regained, problems such as slowed walking speed, a right-left difference between lower limbs in taking a step forward, a right-left difference between lower limbs in muscle strength, spasticity in the paralyzed lower limb, and foot drop are common. In fact, many patients have some residual gait disturbances.

In recent years, the use of gait training devices such as Lokomat and Gait Trainer has drawn attention [2]. For example, body-weight supported treadmill training (BWSTT) is designed for patients with a gait disturbance induced by poststroke lower limb hemiparesis and involves the use of a harness to facilitate gait training on a treadmill while controlling the burden on the paralyzed lower limb. Unlike in cases of poststroke upper limb hemiparesis, however, there are very few reports of the successful application of noninvasive brain stimulation to poststroke lower limb hemiparesis.

Despite this, it may still be possible to use rTMS as a therapeutic intervention against a gait disturbance induced by poststroke lower limb hemiparesis, considering the neuromodulation effects of rTMS. We began attempting application of rTMS to gait disturbance induced by poststroke lower limb hemiparesis. We are already seeing some good signs.

This chapter is about our commitment to the therapeutic application of rTMS to a gait disturbance induced by poststroke lower limb hemiparesis.

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1 Difference between Lower Limb Hemiparesis and Upper Limb Hemiparesis

At least two significant differences exist between poststroke lower and upper limb hemiparesis. First, there is a difference in localization between the lower and upper limb regions of the primary motor area. Known as Penfield's homunculus, the localization of sites in the primary motor area corresponding to each of the body parts is clear. The upper limb region in the primary motor area exists on the lateral surface of the frontal lobe that is located in a shallow area from the surface of the head. In contrast, the lower limb region of the primary motor area is located in the deep, namely, the medial frontal lobe, and areas for the left and right limbs are adjacent to each other (Fig. 5.1). The figure-8 coil used in the treatment of upper limb hemiparesis (p. 10) is considered to have its focus of stimulation at a relatively shallow area. With such a figure-8 coil, however, the magnetic stimulation may be insufficiently delivered to the lower limb region of the primary motor area.

The other difference involves the importance of nerve fibers that derive from the ipsilateral hemisphere and do not cross to the opposite hemisphere. In a healthy

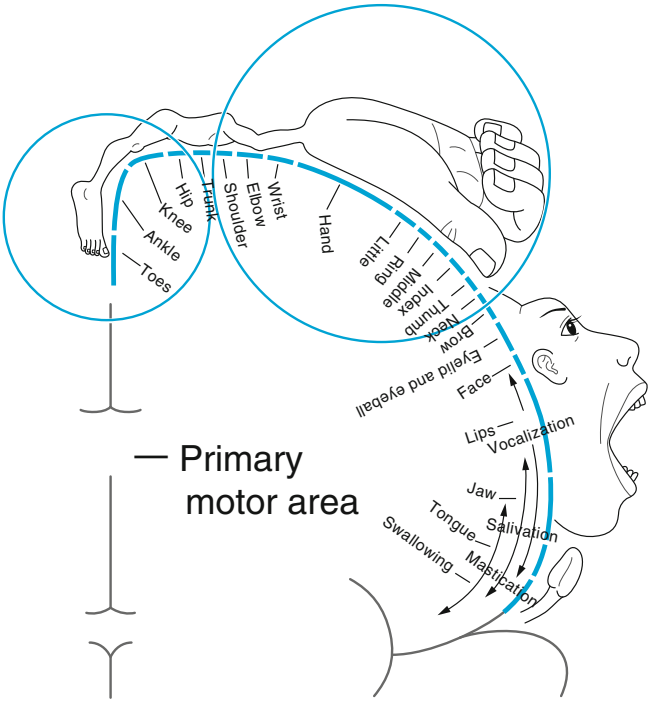


Fig. 5.1 Locations of upper and lower limb regions in the primary motor area. As shown by Penfield's homunculus, the upper limb region exists on the lateral frontal lobe whereas the lower limb region exists deep in the medial frontal lobe

person, most of the motor function in the upper limbs (probably 90 % or more) is governed by the contralateral hemisphere. In other words, the nerve fibers that derive from the contralateral hemisphere and cross through the pyramis medullae oblongatae are considered to govern most of the motor function of upper limbs. However, nerve fibers deriving from the contralateral hemisphere account for only 70–80 % of the motor function of lower limbs while the remaining 20–30 % is considered to be governed by the nerve fibers that derive from the ipsilateral hemisphere and do not cross to the opposite hemisphere (Fig. 5.2) [3, 4].

Some reports have confirmed and demonstrated the importance of the nerve fibers deriving from the ipsilateral hemisphere in the process of recovery from

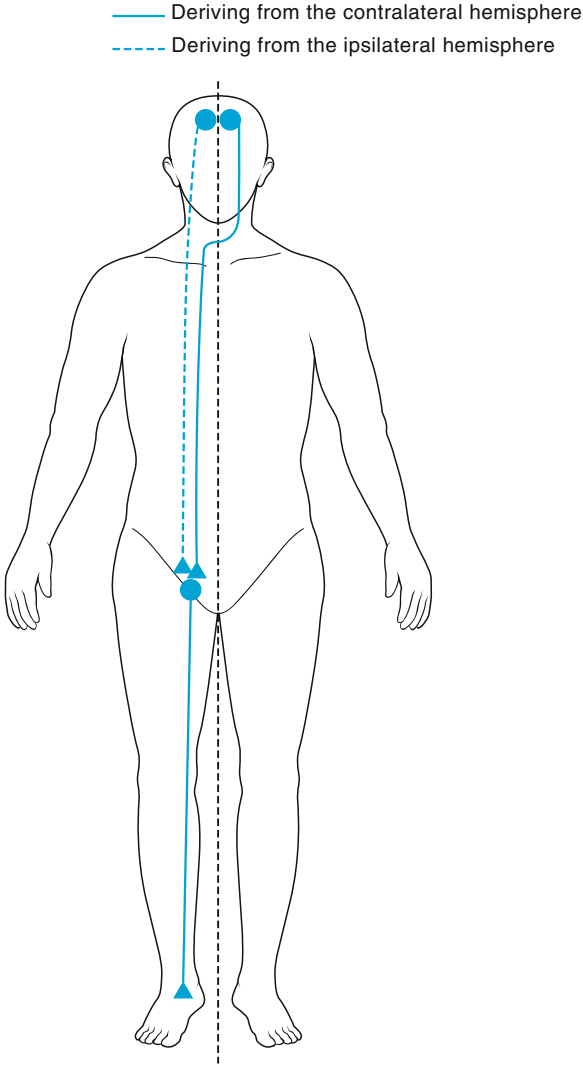


Fig. 5.2 Innervation of the motor function in the lower limbs. To some extent, the motor function in the lower limbs is also governed by the nerve fibers that derive from the ipsilateral hemisphere and do not cross to the opposite hemisphere

poststroke lower limb hemiparesis, with the use of nerve function images. Luft et al. [5] reported that poststroke patients whose gait function achieved remarkable improvement were accompanied by the activation of the primary motor area in the nonlesional hemisphere, which was confirmed by the functional MRI. Enzinger et al. [6] say the degree of activation of the bilateral primary motor area in the functional MRI correlates with the recovery of poststroke gait function. Similarly, Yen et al. [7] discuss the need for activating the bilateral hemisphere in the recovery of poststroke motor function in the lower limbs, based on the study using the TMS mapping.

Considering the differences between the upper limb and the lower limb motor system, it may be necessary to ensure that "the magnetic stimulation reaches the lower limb region of the primary motor area which is located in a deep area," provided that rTMS is to be therapeutically applied to poststroke lower limb hemiparesis. It may also be necessary to "activate the lower limb region of the unaffected primary motor area in addition to the lower limb region of the affected primary motor area."

In response to this, a double cone coil has been clinically applied in recent years. This is a set of two circular coils connected with each other at an angle ranging between 90 and 120 degrees. It is designed to have a deep focus of stimulation, namely, the point at which the magnetic stimulation concentrates (Fig. 5.3). The safety of the double cone coil in a human body has already been demonstrated. Using this coil is also reported to facilitate magnetic stimulation in the lower limb region of the primary motor area. According to Stokić et al. [8], using the double cone coil to give stimulation to a healthy person made it possible to record the MEP from the lower limb muscles such as tibialis anterior. Terao et al. [9] published a similar report.

Based on these findings, it is quite possible that the application of the double cone coil on the cranial median line, as shown in Fig. 5.4, could simultaneously stimulate the lower limb regions of the bilateral primary motor area.

Fig. 5.3 Double cone coil. This coil is designed to have a focus of stimulation in a deep position. The coil in the photo is Cool D-B80 (manufactured by MagVenture)

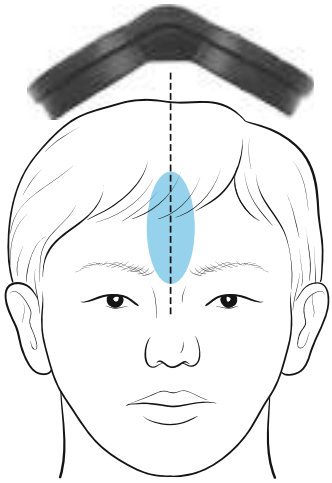


Fig. 5.4 Application of the double cone coil. Applying the coil on the cranial median line enables to simultaneously stimulate the lower limb regions of the primary motor area on both sides

2 Usefulness of High-Frequency rTMS with the Use of a Double Cone Coil

Based on the abovementioned view, we decided to conduct a crossover study to learn how the high-frequency rTMS on the lower limb region of the primary motor area on both sides of the cerebrum using a double cone coil influences the gait function of poststroke patients with lower limb hemiparesis. In other words, we sought to clarify the effects of high-frequency rTMS on gait functions by applying high-frequency rTMS using a double cone coil and sham stimulation on all patients and evaluating their gait function before and after each stimulation [10].

A. Patients

The study enrolled 18 patients with a gait disturbance and chronic poststroke hemiparesis. The eligibility criteria were set as shown in Table 5.1 in consideration of the guidelines of Wassermann [11] and similar. Table 5.2 shows the clinical background of the patients. The mean age of patients was 52.1 years old, and the mean time from onset to study enrollment was 52.8 months. The causal type of stroke was intracerebral bleeding in 13 patients and cerebral infarction in 5 patients.

B. Methods

The study was designed as a crossover study in which all patients receive both high-frequency rTMS and sham stimulation for 20 minutes each. In other words, half of the patients received the high-frequency rTMS and had an interval of at least 24 hours

Table 5.1 Eligibility criteria for indication of rTMS treatment for lower limb hemiparesis

1. Although an onset of stroke has induced a gait disturbance, the patient is capable of walking at least 10 meters by themselves without using a cane or a walking aid
2. The age between 30 and 70 at the time of the study
3. Time between the stroke onset and the study enrollment of more than 12 months
4. History of a single stroke only (neither recurrent nor bilateral)
5. No active systemic or mental illness requiring medical management
6. The patient has not received motor point block, botulinum toxin or other procedure for local treatment of lower limb spasms
7. The patient has no history of spasticity
8. No abnormality is recognizable in an electroencephalography
9. No abnormality is The patient has no contraindications specified in the Wassermann's guideline (intracranial metals, a cardiac pacemaker and pregnancy) in an electroencephalography

As of December 2012

Table 5.2 Clinical background of patients[a]

Age		52.1 ± 11.9 years old
Time from the onset of stroke		52.8 ± 30.7 months
Gender	Men	13 (72 %)
	Women	5 (28 %)
Type of stroke	Intracerebral hemorrhage	13 (72 %)
	Cerebral infarction	5 (28 %)
Site of lesion	Cerebrum	16 (89 %)
	Brain stem	2 (11 %)
Paralyzed side of lower limb	Right lower limb hemiparesis	12 (67 %)
	Left lower limb hemiparesis	6 (33 %)
Lower limb BRS	Stage III	5 (28 %)
	Stage IV	6 (33 %)
	Stage V	7 (39 %)

[a] $n = 18$

before receiving sham stimulation. The remaining patients received sham stimulation first and had the same interval before receiving high-frequency rTMS (Fig. 5.5). The patients' gait function was assessed before and after each type of stimulation.

The application of high-frequency rTMS involved the use of MagPro R30 and a double cone coil (manufactured by MagVenture) (Fig. 5.6). Ten-second stimulation at 10 Hz was performed every 60 seconds (in other words, at 50-second intervals). This was repeated 20 times within 20 minutes (Fig. 5.7). Stimulation was given to an area on the cranial median line in which the MEP of the tibialis anterior of the unaffected lower limb is most remarkably induced. The intensity of stimulation was set at 90 % of the motor threshold of the tibialis anterior. For sham stimulation, a double cone coil was vertically applied to the same area as in the high-frequency

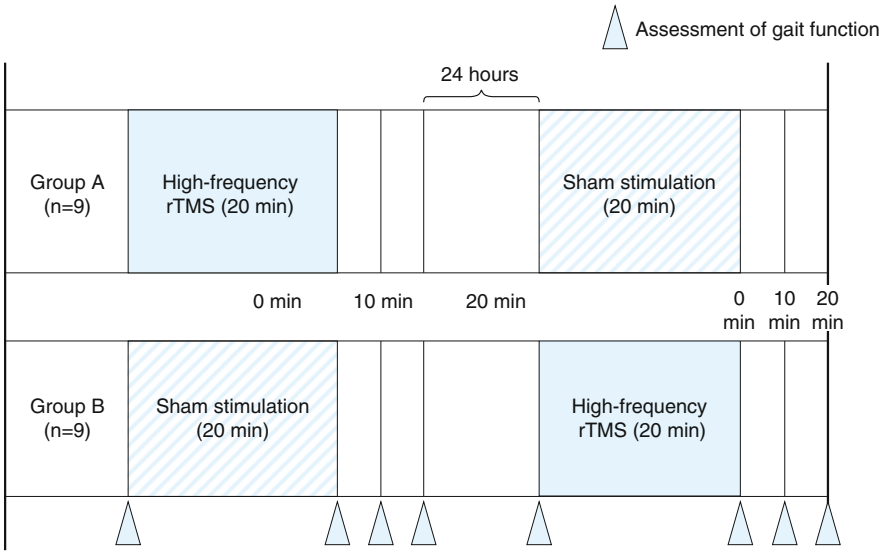
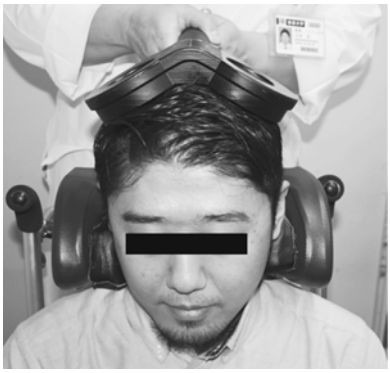


Fig. 5.5 Design of a crossover study. All patients receive both the high-frequency rTMS and sham stimulation for 20 minute each

Fig. 5.6 Application of high-frequency rTMS. A double cone coil is fixed on the cranial median line



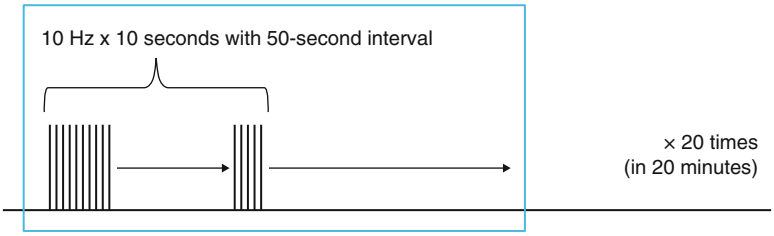


Fig. 5.7 Protocol of high-frequency rTMS. Repeat 10-second stimulation at 10 Hz with 50-second intervals

rTMS so that the coil surface would face forward, not downward. In this way the same stimulation as that in high-frequency rTMS was given for 20 minutes.

Gait function was assessed by determining the walking speed and physiological cost index (PCI) four times: immediately before stimulation, immediately after stimulation, 10 minutes and 20 minutes after completion of stimulation, for each type of stimulation. Walking speed was determined by having a patient walk 10 meters as fast as possible. PCI is an index of gait efficiency, and the smaller the PCI is, the better his/her gait efficiency is considered to be. The study used the following formula [heart rate (beat/minute), walking speed (meter/minute)] to calculate PCI based on the values before and after a 10-meter walk.

C. Results

High-frequency rTMS for 20 minutes was applied to all patients without the incidence of adverse events.

Walking speed was significantly higher in the high-frequency rTMS group than in the sham stimulation group immediately after 20-minute stimulation. The difference remained until 20 minutes after completion of stimulation (Fig. 5.8) [10].

PCI was significantly higher in the high-frequency rTMS group than in the sham stimulation group immediately after stimulation. However, the difference between the groups was not significant at 10 minutes or 20 minutes after completion of stimulation (Fig. 5.9) [10]. As a result of statistical processing, no carryover effect

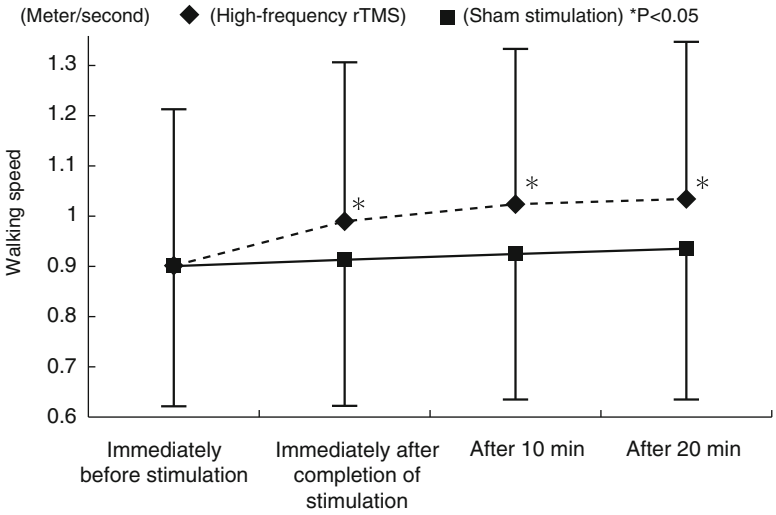


Fig. 5.8 Change in walking speed after stimulation. Walking speed was significantly higher in the high-frequency rTMS group than in the sham stimulation group until 20 minutes after completion of stimulation [10]

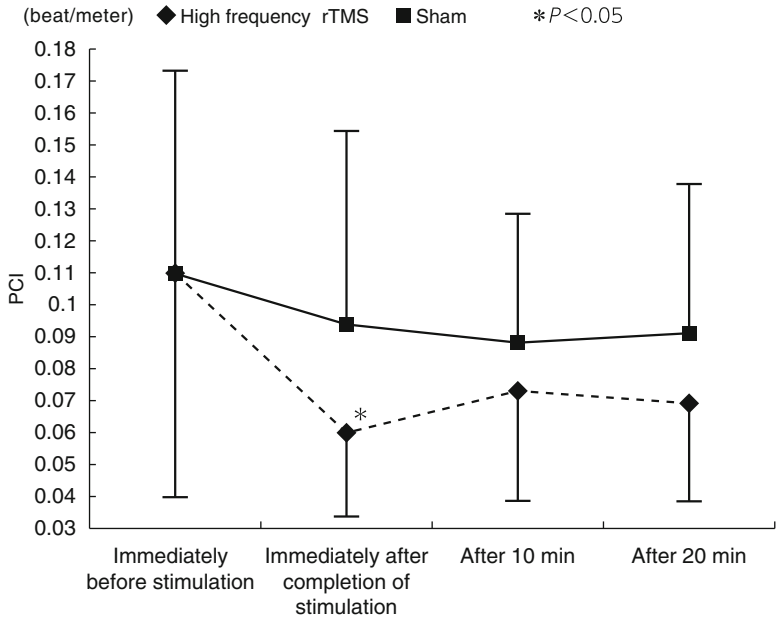


Fig. 5.9 Changes in PCI after stimulation. Only immediately after stimulation was PCI significantly higher in the high-frequency rTMS group than in the sham stimulation group [10]

was recognizable between high-frequency rTMS and sham stimulation. This led to a conclusion that the crossover study had been properly conducted.

These results may be interpreted as a possibility that high-frequency rTMS on the lower limb region of the bilateral primary motor area with the use of a double cone coil may quickly ameliorate the gait function of poststroke patients with hemiparesis. However, the absence of carryover effect between the types of stimulation led to a conclusion that the effects of the 20-minute high-frequency rTMS did not last 24 hours, (predetermined interval between two types of stimulation). One of the reasons why the change in PCI after the application of high-frequency rTMS was transient and its effects were not satisfactory is that PCI, the calculation of which should be based on the heart rate before and after several minutes' walking, was determined before and after only a 10-meter walk. This made changes in the heart rate less likely.

3 Protocol of Combined Use of High-Frequency rTMS and Intensive Physical Therapy

These findings led to the estimation that high-frequency rTMS on the lower limb region of the bilateral primary motor area with the use of a double cone coil would benefit the gait function of stroke patients with lower limb hemiparesis. For

20-minute single rTMS stimulation, however, the possibility that the benefits would not last long was also suggested.

Therefore, we devised a therapeutic protocol for "repeated use of rTMS in combination with intensive physical therapy (PT)," a concept similar to "a combination treatment of rTMS and intensive OT against upper limb hemiparesis (NEURO-15)." In other words, this concept aims at facilitating a functional reorganizing in the lower limb region of the primary motor area by performing high-frequency rTMS with the use of a double cone coil to enhance the plasticity of lower limb region of the bilateral primary motor area before performing intensive PT. The following describes the current facts of efforts for the new combination treatment.

A. Patients

The patients are the same as the abovementioned crossover study. The study enrolled stroke patients with gait disturbance and did not enroll those with severe gait disturbance who always needed a cane or an orthosis and/or had difficulty walking even 10 meters.

B. Methods

The combination treatment was performed as a 13-day protocol for hospitalization treatment (Table 5.3). A concomitant therapy consisting of 20-minute high-frequency rTMS and 60-minute intensive PT was performed in two sessions every day except the day of admission/discharge and Sundays.

Table 5.3 An example of hospitalization schedule for rTMS treatment for lower limb hemiparesis[a]

	Mon.	Tuesday through Saturday	Sun.	Monday through Friday	Sat.
Morning	Admission	High-frequency rTMS (20 minutes)	No treatment	High-frequency rTMS (20 minutes)	Post-treatment evaluation
		Intensive PT (60 minutes)		Intensive PT (60 minutes)	
Afternoon	Pre-treatment evaluation	High-frequency rTMS (20 minutes)		High-frequency rTMS (20 minutes)	Discharge
		Intensive PT (60 minutes)		Intensive PT (60 minutes)	

[a]An example of being hospitalized on Monday
The actual hospitalization schedule is adjusted by each institution
As of December 2012

The application of high-frequency rTMS was the same as in the abovementioned crossover study. In one session, 10-second stimulation at 10 Hz using a double cone coil was repeated 20 times in 20 minutes. The site of stimulation would be the area in which MEP of tibialis anterior of the unaffected lower limb on the cranial median line would most remarkably be induced. The intensity of stimulation would be 90 % of motor threshold of the tibialis (Table 5.4).

One session of intensive PT consisted of one-on-one training session with a physical therapist for 60 minutes. The program included a few minutes of warm-up on the mat, followed by 5–10 minutes of stretching exercise, 5–10 minutes of rising training aimed at increasing muscular strength in the lower limbs, and 25–35 minutes of treadmill training without a relief. Walking speed (exercise intensity) on the treadmill was designed to correspond to Level 4 (somewhat hard) of the modified Borg scale, although this would be adjusted to the patient's gait condition whenever necessary.

C. Results

As of December 2012, the combination treatment has already been performed in more than 20 patients. To date, none of the patients who completed the 13-day protocol experienced any adverse events or adverse reactions of special interest. The protocol was judged to be safe. A comparison between the day of admission and the day of discharge in terms of the effects on gait function suggested improvements in multiple parameters such as walking speed and PCI.

On an individual basis, the amelioration of talipes varus and plantar flexion of the paralyzed lower limb was recognized in many patients. Improvements in toe clearance have also been recognized. Some patients reported subjective changes such as "ease in moving the paralyzed lower limb" and "a feeling that the paralyzed lower limb is lighter than before" (although these were subjective estimations). Substantial differences in walking speed and in the degree of PCI improvement were recognizable among patients.

Table 5.4 An example of hospitalization schedule for rTMS treatment for lower limb hemiparesis[a]

Coil used	Double cone coil
Site	Bilateral cerebrum (lower limb region of the primary motor area)
Intensity	90 % of motor threshold
Frequency	High-frequency rTMS (10 Hz)
Duration	1 session lasting 20 minutes (2000 pulses), twice daily
No. of days at hosp.	13 days

[a]The actual treatment is adjusted by each institution

As of December 2012

4 Future Challenges

As mentioned, high-frequency rTMS on the lower limb region of the bilateral primary motor area using a double cone coil may be a beneficial means of therapeutic intervention in poststroke lower limb hemiparesis. At this point, however, establishing this as a therapeutic intervention requires at least the following issues to be solved.

1) Intensity of rTMS

The study determined the intensity of rTMS based on the motor threshold of the tibialis anterior of the nonparalyzed lower limb. This procedure would make it possible to determine the motor threshold and the intensity of stimulation in almost all patients. In a condition such as serious damage to the nerve pathway connecting the lesional hemisphere to the paralyzed lower limb, the stimulation may be insufficient (too weak) against the primary motor area of the lesional hemisphere. Because of this, the determination of intensity of stimulation may also require consideration of the motor threshold of the muscle of the paralyzed lower limb.

2) Details of the PT Program for Combined Use with rTMS

At present, we use the PT program, the core of which is gait training on a treadmill, in combination with high-frequency rTMS. It is quite possible that this training program is not optimal. For example, increasing the proportion of an exercise for strengthening the lower limb muscles would be better. Determining "a more optimal PT program" for combined use with rTMS would help increase the benefits of rTMS.

3) Introduction of a Gait Analysis

The recent study showed that the application of high-frequency rTMS using a double cone coil would ameliorate gait function. However, the mechanism has yet to be elucidated. Doing so may require a gait analysis and a motion analysis to be performed over time.

4) Application of Brain Function Imaging

It may be expected that the amelioration of the gait function after the application of high-frequency rTMS using a double cone coil will be followed by a certain plastic change in the lower limb region of the primary motor area or its surrounding tissue.

However, this has not been searched by brain function imaging such as functional MRI (fMRI) and PET.

5) Necessity of a Randomized Controlled Trial

Showing evidence of the usefulness of concomitant therapy with high-frequency rTMS and intensive PT requires RCT to compare the "high-frequency rTMS + intensive PT group" and "sham stimulation + intensive PT group."

The rTMS treatment for gait disturbances induced by poststroke lower limb hemiparesis is still in a developmental stage and needs further improvement. As far as our findings suggest, however, it is quite possible that the application of high-frequency rTMS using a double cone coil to the lower limb region of the primary motor area becomes one of the new treatment options for lower limb hemiparesis and gait disturbances.

Appendix: Intensive Physical Therapy That Should Be Used in Combination with rTMS

Lower Limb Dysfunction and PT in Poststroke Hemiparesis

The following discusses a mechanism that may occur if rTMS on an upper limb has influenced lower limb function.

In PT, the severity of poststroke hemiparesis is determined by the Brunnstrom recovery stages (BRS) (Table 5.5) [12, 13]. The staging is intended to facilitate judgment on whether or not a limb can move and perform isolated movement. In a normal condition of "isolation," the person can do a simple exercise and move his/her hands, legs, and fingers independently at will. Separation can be an important criterion to decide whether a limb is in a normal condition. Nonisolation does not always mean a state in which a limb cannot move at all.

In BRS, Stage IV or higher means isolation is recognizable. However, it is hard to discern the conceptual reduction of spasticity from the expression of isolation. Judgments as rule of thumb cannot be ruled out. If the muscle tone has increased, it is often the case that the expression of isolation is inadequate. In particular, it has much to do with factors such as posture, action, and move. Under load, abnormality of muscle tone uniformly becomes apparent. Differences between Stage IV and V should be decided by observing the same joint movement performed in different postures. In other words, this means isolation is strongly influenced by an increase in postural muscle tone.

The postural muscle tone allows a hemiparesis patient to move the upper limb, which is relatively relaxed in a supine position, to take a specific posture in the upright position or while walking.

This is the so-called Wernicke-Mann leg position. Its characteristics are more apparent in a sitting position than in a supine position and while walking than while

Table 5.5 Brunnstrom recovery stage (lower limbs and trunk)

Stage	Lower limbs and trunk
I	[Flaccidity] Neither muscle contraction nor movement is possible reflexively or voluntarily
II	[Spasticity occurrence period] Muscle contraction occurs from an associative reaction or voluntarily (elements of synergy slightly occur)
III	[Remarkable spasticity] Synergy or some of its elements occurs voluntarily. Synergy with flexion and extension
IV	[Spasticity slightly reduced] A patient can do an exercise that is slightly separated from synergy In a sitting position, a patient can flex the knee by 90 degrees or more and slide the sole backward along the floor In a sitting position, a patient can dorsiflex the foot with the heel remaining in contact with the floor
V	[Spasticity reduced] A patient can do an exercise that is considerably separated from synergy In an standing position, a patient can place the hip joint in an extended position and flex the knees In an standing position, a patient can extend the foot slightly forward and dorsiflex the ankle joint with the heel remaining in contact with the floor
VI	[Minimum spasticity] In an standing position, a patient can abduct the hip joint while keeping the knee extended In a sitting position, a patient can alternately contract the inner and outer knee flexors

Excerpted from Refs. [12] and [13]

sitting. An increase in the muscle tone in the upper limb influences movements of the trunk and lower limbs.

A gait of a human being is phylogenetically differentiated from that of other vertebrates by the movement of the trunk when crawling on hands and knees. This can be explained, in an arthrokinematic manner, as a smooth and alternate rolling and sliding movement based on the retention of centripetal force, and kinematically as a phase movement where the limbs swing alternately. When an upper limb swings forward, the lower limb on the opposite side makes a step forward. When an upper limb swings backward, the lower limb on the opposite side is guided to the toe-off position through the stance phase. In other words, a gait consists of regular movements in which upper limbs and lower limbs move in opposite phases. A forward movement is accompanied by an axial rotation around the trunk (Fig. 5.10).

Opposite phases with left-right alternate movements require the upper limbs to swing and the lower limbs to take a step. The more poststroke hemiparesis makes isolation insufficient, the more it strategically supplements a compensatory function that replaces the functions of the upper limbs and trunk that are necessary for walking. Worse, abnormality in muscle tone makes it hard to form a smooth cycle. As a consequence the gait cannot be symmetrical, and the gait of the patient with stroke takes on characteristic patterns such as extension thrust pattern (a pattern in which

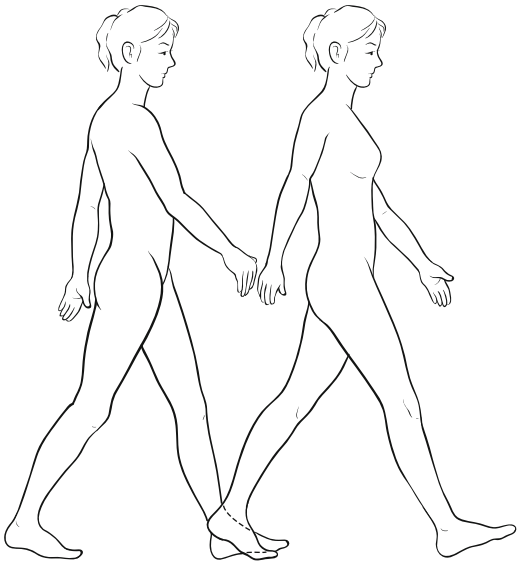


Fig. 5.10 Opposite phases of a human gait. When the left leg makes a step forward, the right hand swings forward. When the right leg makes a step forward, the left hand swings forward

the knee is overextended), stiff knee pattern (a pattern in which a stiff knee results in less flexion), and bucking knee pattern (a pattern in which the knee is overflexed). An abnormal gait pattern lacks efficiency and burdens the cardiopulmonary function. As a consequence, the patient slows walking speed to stabilize, and the possibility of secondary complications such as falls and pain increases.

Here, it is worth noting that the effects of rTMS treatment demonstrated by Abo et al. [14–18] through a study with a rat model can be explained as follows: functional compensation in the lesional hemisphere and in the residual regions around the lesion, not in the nonlesional hemisphere on the nonlesional side, plays an important role in the partial involvement within an adult's brain that concerns recovery from paralysis. For tissues around the lesion of the affected brain that are considered to facilitate functional recovery, low-frequency stimulation on the nonlesional hemisphere is reported to have reduced interhemispheric inhibition and activated functional compensation.

In fact, the effects of rTMS on upper limb hemiparesis are reported. Given the above mechanism of a human gait, the effects of rTMS on reducing muscle tone in the upper limbs may also bring about a change in gait that requires coordination of the upper and lower limbs.

Usefulness of Treadmill Gait Training

A gait is an unconscious movement and is based on a reflexive mechanism. It is considered that a gait can be divided into three different phases as a stratified control (Fig. 5.11) [19]. The first phase involves planning and preparation for movements in

the cerebrocortical motor area. The second phase involves coordination by the brain stem. The third phase is characterized by control by the central pattern generator (CPG) consisting of a group of spinal interneurons. CPG does not involve voluntary control by the cerebrum and is coordinated in a reflexive manner. While walking, a person does not think about when to move the other leg forward every time he or she takes a step. Every step is not based on intentional adaptation to a command to contact the ground or floor with a heel. Voluntary control by the cerebrum is limited to adaptation to a signal or changes in road surface, unevenness of the floor or ground, and similar.

When walking on a flat surface, a patient with hemiparesis moves a leg forward and contacts the ground or floor with a good clearance and keeps the feet supporting the body to prevent falls, before shifting his/her center of gravity toward the opposite side, the nonparalyzed lower limb. While walking, a patient with hemiparesis remains conscious about these procedures. In particular, consciousness about these procedures is greater in patients with problems such as sensory impairment, weakened muscle strength in the nonparalyzed lower limb, and fear that comes from advanced age. These people are more likely to stop walking before stepping over a bump or passing someone. Many of these people walk asymmetrically by leaning the trunk forward and leaning the pelvis backward to flex the hip joint with a center of gravity on the nonparalyzed lower limb. Even the coordination of pace is based on the patient's will. It is not always the case that doing a lot of walking every day will facilitate recovery. To induce a qualitative

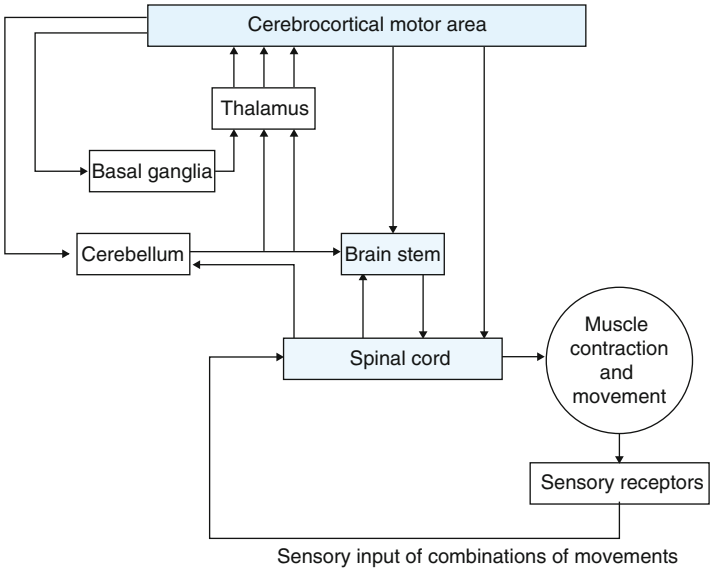


Fig. 5.11 Diagram of stratified control [8]

effect, a physical therapist gives visual stimulation with the use of oral instructions, a mirror or a video, shows changes in time-distance factors, and combines them with handling in an effort to bring about alteration. In fact, the authors do this in clinical practice. It is difficult to scientifically verify this type of intervention in a gait.

On the other hand, walking on a treadmill involves the floor surface shifting backward at a constant speed, providing a kind of gait using passive stepping. In terms of floor reaction force waveform overall, walking on a treadmill involves greater similarity than walking on a flat surface does [20]. Despite differences in minor parameters, it is considered to be possible to diagnose and determine the degree of amelioration of gait disturbances with the use of a treadmill [21].

For a period of time after starting a treadmill, the patient continues to focus on movements (stimulation) on the floor surface and may feel insecure at times. Since the treadmill gait training is provided in a stepwise manner, the patient gradually adapts him/herself to the changeless and constant stimulation. This may facilitate a shift from the conscious movements of legs to unconscious movements. This is a clear difference from walking on a flat surface where stimulation occurs randomly and in many different forms. It is also important that the treadmill gait training ensures physical therapists sufficient time for observation.

Studies of paraparesis induced by spinal cord injury have confirmed some effects of walking on a treadmill. For example, walking on a treadmill may exert effects in the form of induction of muscle activity in harmony with a walking cycle [22] or achievement of a hip extension position in the late stance phase [23]. In addition, using a treadmill serves as an opportunity for a hemiparesis patient to become aware of a left-right gap in his/her gait cycle. In patients whose muscle tone in the upper limb has been reduced after rTMS, using a treadmill may influence upper limb swings and the rotation of a trunk and, consequently, make it possible to swing a lower limb and to achieve a standing position within an area of hip joint extension. Compared with walking on a flat surface that is a patient-steering movement, walking on a treadmill is a passive movement adapted to an automatically moving surface. The use of a treadmill may be expected to help improve ambulatory ability through the indirect effects of reduction of muscle tone in the upper limbs and trunk, provided that rTMS has reduced the tension in the upper limbs and made it easier for isolation to express.

In today's healthcare and welfare practices, aggressive PT is becoming increasingly hard to perform with patients in the maintenance period. Many patients engage in self-exercise as a part of their daily life. The Japanese Guidelines for the Management of Stroke 2009 [24] recommends rising and walking for rehabilitation in the maintenance period. However, it is hard for a patient alone to concentrate on a specific instruction without receiving advice. This is especially true for patients with hemiparesis in the generation to which long-term care insurance services do not apply. We hope that rTMS will play the role of a means of preconditioning in performing intensive PT for patients who continue training on their own.

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Chapter 6
rTMS in the Acute Phase of Stroke

Introduction

There are many reports on the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for the treatment of stroke worldwide, and in recent years rTMS has become the most promising field of neurohabilitation. However, the overwhelming majority of these reports are on the application of rTMS for the treatment of upper extremity paralysis in the chronic phase of stroke, and there are only few reports on studies in which rTMS was used in acute stroke patients (Table 6.1) [1–13]. There are two main reasons why research on the use of rTMS for the treatment of acute stroke patients still lags. One is safety, namely, the fear of epileptic seizures, which is one of the risks that are associated with rTMS therapy. Epileptic seizures in acute stroke are an independent prognostic factor for in-hospital mortality, and therefore a cautious evaluation of the appropriateness of rTMS application is required [14]. Another reason is the study design. Obviously, spontaneous recovery plays an important role in acute stroke, and therefore for detecting the effects of rTMS it is necessary that patients are selected based on strict criteria or that the study is conducted with a large number of patients. Moreover, such studies must have a randomized controlled trial (RCT) or a crossover trial (COT) study design. In recent years, there has been a tendency to question whether therapeutic intervention studies that are expected to be highly beneficial are ethically justifiable as far as the control group is concerned, when they are conducted as a RCT. Meanwhile, COTs extend the intervention period and therefore can be said not to be suited as a clinical research method in acute hospitals that aim to shorten the duration of hospitalization.

The difficulty of conducting therapeutic intervention studies that involve acute stroke patients is not limited to rTMS alone. In a review by Stinear et al. from 2013, only 30 intervention studies on the rehabilitation (in the following referred as reha) of motor disorders after acute stroke are rated as high-quality studies, and it is described that there are only 5 research papers on rTMS, including a research paper

M. Abo, W. Kakuda, *Rehabilitation with rTMS*,
DOI 10.1007/978-3-319-20982-1_6

Table 6.1 List of rTMS intervention studies for acute phase of stroke to date [1–13]

Authors	Year of publication	Number of subjects	Summary
Khedr EM, et al. [1]	2005	26	ADL was improved by rTMS
Liepert J, et al. [2]	2007	20	Upper limb function was improved by rTMS of 1 Hz
Di Lazzaro V, et al. [3]	2008	12	The activity of the cerebral cortex on the lesional side was enhanced by either cTBS or iTBS
Khedr EM, et al. [4]	2009	36	Upper limb function was improved by rTMS of 1 and 3 Hz. In particular, the improvement lasted until three months later when rTMS of 1 Hz was performed
Khedr EM, et al. [5]	2010	48	Upper limb function was improved by rTMS of 1 and 3 Hz
Khedr EM, et al. [6]	2010	22	Dysphagia due to the brainstem infarction was improved by rTMS of 3 Hz and the improvement lasted until two months later
Khaleel SH, et al. [7]	2010	31	The cerebral blood flow in the MCA region was improved by rTMS of 10 Hz over DLPFC
Chang WH, et al. [8]	2010	28	Upper and lower limb motor function and ADL were improved by rTMS of 10 Hz
Hsu YF, et al. [9]	2013	12	Upper limb function was improved by iTBS
Sasaki N, et al. [10]	2013	29	Upper limb function was improved by rTMS of 1 and 10 Hz. In particular, greater improvement was observed when rTMS of 10 Hz was performed
Kim BR, et al. [11]	2013	27	As a result of comparing the effect of rTMS of 1 and 10 Hz over USN, improvement was observed when rTMS of 10 Hz was performed
Kim WS, et al. [12]	2014	32	Balance was improved in patients with cerebellar ataxia when rTMS of 1 Hz was performed
Sasaki N, et al. [13]	2014	58	Upper limb function improved further when rTMS of 1 and 10 Hz was performed simultaneously than when only rTMS of 10 Hz was performed

rTMS repetitive transcranial magnetic stimulation, *cTBS* continuous theta-burst stimulation, *iTBS* intermittent theta-burst stimulation, *DLPFC* dorsolateral prefrontal cortex, *MCA* middle cerebral artery, *ADL* ability of daily living, *USN* unilateral spatial neglect

by the authors [15]. However, all consider the effectiveness of rTMS in acute stroke patients to be positive, and also the meta-analysis by Hsu et al. showed that the effectiveness of rTMS when used for improving upper extremity paralysis is higher in acute stroke than in chronic stroke patients (effect size: chronic stroke 0.66, acute stroke 0.79) [16]. In this report we will briefly introduce the results of two studies on the use of rTMS for the treatment of upper extremity paralysis in acute stroke patients that we reported to date.

Which rTMS Modality Is More Beneficial for Acute Stroke, High- or Low-Frequency rTMS?

I will reserve details on the principles of rTMS for a future occasion. In short, there are basically two types of rTMS, stimulatory high-frequency rTMS (HF-rTMS) and inhibitory low-frequency rTMS (LF-rTMS). For the treatment of upper extremity paralysis in the chronic phase of stroke the following rTMS methods can be used. A method that improves paralysis by enhancing the activity of the lesional hemisphere through interhemispheric inhibition (IHI) resulting from inhibition of the overactivity of the nonlesional hemisphere, which can be achieved by applying LF-rTMS (this method is similar to the NovEl Intervention Using Repetitive TMS and Intensive Occupational Therapy [NEURO] [17] that is conducted at the Department of Rehabilitation Medicine of Jikei University School of Medicine), and a method that directly activates the lesional hemisphere by applying HF-rTMS (Fig. 6.1). First we examined the effectiveness of these two types of rTMS when used for the treatment of upper extremity paralysis in acute stroke patients [10].

1) Patients and Methods

This study involved 29 patients with newly developed acute-stage cerebral infarction or cerebral hemorrhage (mean age at the time of hospitalization: 65 ± 10 years old, 13 cerebral infarction, 16 cerebral hemorrhage) who had lesions in the unilateral

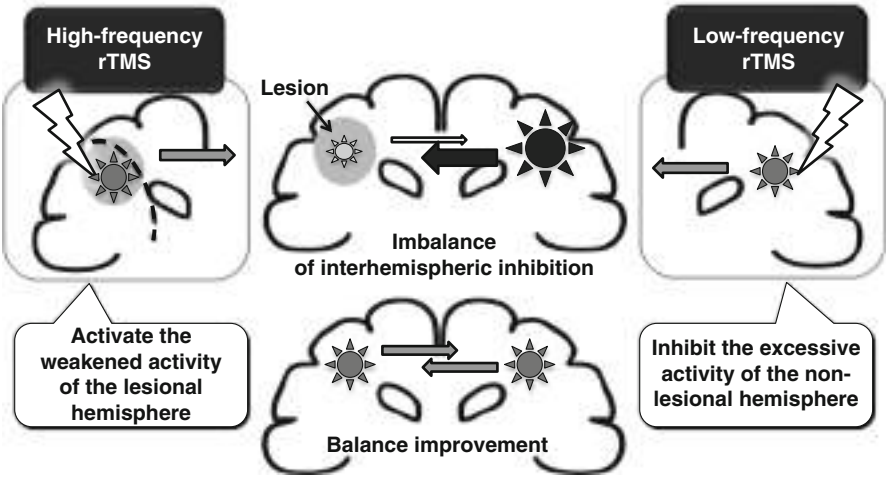

Fig. 6.1 There are two methods for improving the disrupted balance between the two hemispheres that is caused by interhemispheric inhibition resulting from unilateral hemispheric stroke: high-frequency rTMS (HF-rTMS) for activating the decreased function of the lesional hemisphere and low-frequency rTMS (LF-rTMS) for inhibiting the overactivity of the nonlesional hemisphere

middle cerebral artery territory that did not include the cortex. Patients hospitalized 6 hours or more after the onset of stroke, patients who had been administered tissue plasminogen activator (tPA), patients who had undergone surgery, and patients with severe disturbance of consciousness were excluded from the study. Subjects were randomly allocated to the HF-rTMS group (9 subjects), LF-rTMS group (11 subjects), and sham stimulation group (9 subjects), and within 30 days after onset of stroke (mean 17.4 ± 5.4 days), 1 stimulation session was conducted each day for 5 consecutive days as described below. During these 5 days before and after intervention changes in the grasping power (GP) of the paralyzed hand and fingers, and tapping frequency (TAP) within 30 seconds were compared between the 3 groups.

2) Application of rTMS

The site at which maximum flexion of the contralateral index finger was achieved following primary motor cortex stimulation through single-pulse TMS was set as rTMS stimulation site, and stimulation intensity was set at 90 % of the minimum stimulation intensity at which index finger flexion was achieved. During 1 session, in the HF-rTMS group 10-Hz rTMS trains were applied for 10 seconds to the stimulation site on the lesional side followed by a pause of 50 seconds, and this was repeated 10 times. In the LF-rTMS group 1-Hz rTMS trains were applied for 30 minutes to the stimulation site on the nonlesional side. In the sham stimulation group a stimulation coil was placed vertically toward the skull surface in such a way that no magnetic flux penetrated the brain, and the nonlesional hemisphere was stimulated at a frequency of 1 Hz (so that only the sound of stimulation could be heard) for 10 minutes.

3) Results

Prior to intervention there were no differences between the three groups regarding the clinical characteristics of the patients, stroke severity, or severity of paralysis. No adverse events were observed in any of the patients who participated in this study, and the study protocol could be completed. During the 5 days of intervention no significant changes in GP and TAP were observed in the sham stimulation group; however, in both the HF-rTMS group and the LF-rTMS group a significant improvement of GP and TAP was observed (Fig. 6.2). GP was 0.6 ± 0.7 kg in the sham stimulation group, 4.2 ± 2.8 kg in the HF-rTMS group, and 2.3 ± 2.9 kg in the LF-rTMS group, and thus when comparing the increase in GP among these three groups, in the HF-rTMS group a significantly greater increase in GP was observed than in the sham stimulation group. TAP was 2.8 ± 4.1 times in the sham stimulation group, 12.3 ± 8.7 times in the HF-rTMS group, and 14.3 ± 15.1 times in the LF-rTMS group, and thus also the increase in TAP was significantly greater in the HF-rTMS group than in the sham stimulation group (Fig. 6.3).

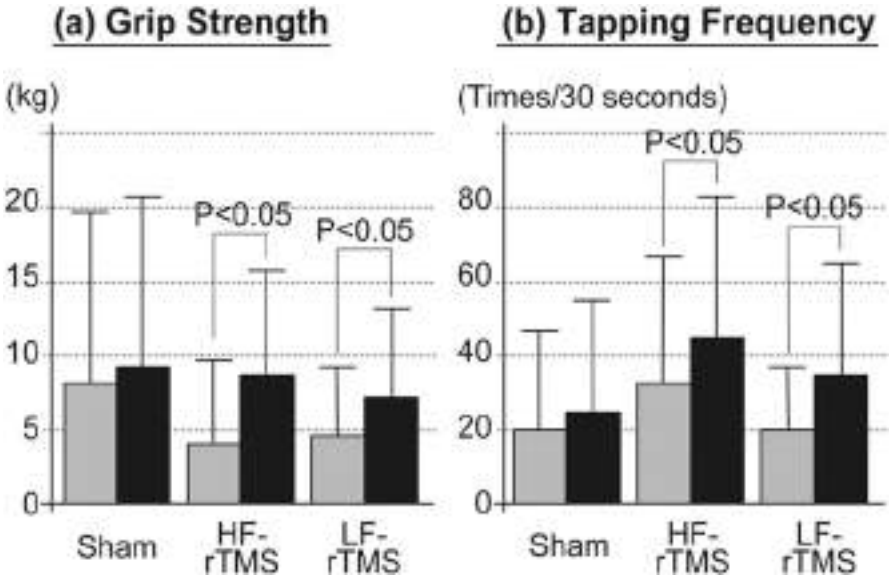

Fig. 6.2 When comparing grip strength and tapping frequency before and after rTMS intervention for a period of 5 days, in the sham stimulation group no significant improvement was observed either for grip strength or for tapping frequency; however, in both the HF-rTMS group and LF-rTMS group a significant improvement was observed for both grip strength and tapping frequency

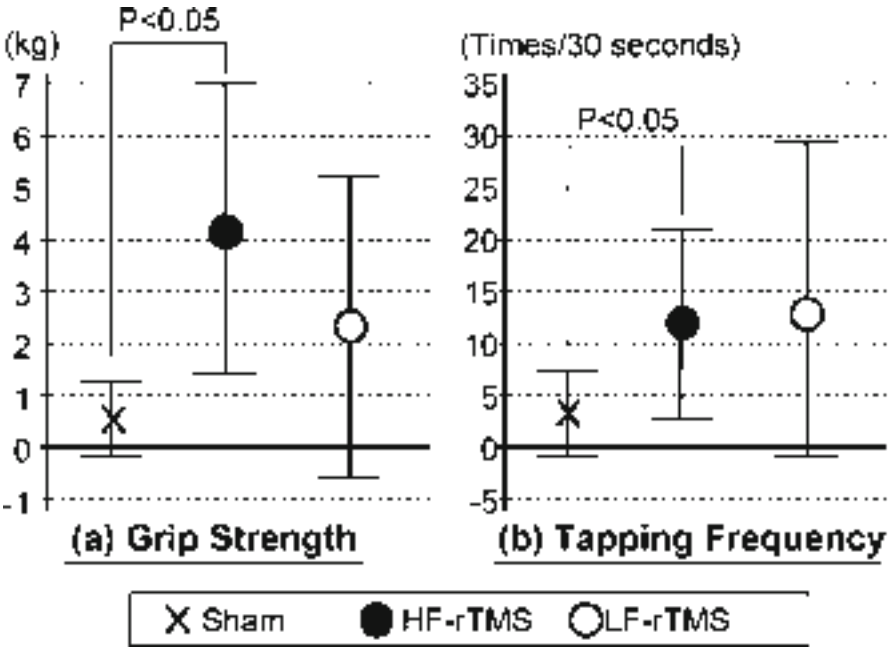

Fig. 6.3 A comparison of changes in grip strength and tapping frequency following rTMS intervention for a period of 5 days showed that only in the HF-rTMS group changes in grip strength and tapping frequency were significantly greater than in the sham group

Is Bilateral rTMS More Beneficial for Acute Stroke than High-Frequency rTMS?

Next, we thought that probably a stronger effect could be achieved if HF-rTMS and LF-rTMS were applied simultaneously and devised a method for conducting bilateral rTMS (BL-rTMS) by using two rTMS devices. Then we compared the results obtained with BL-rTMS and those obtained with unilateral HF-rTMS, which showed better results than the other stimulation methods in the previous study described above [13].

1) Patients and Methods

This study involved 58 patients with acute-stage cerebral infarction or cerebral hemorrhage who fulfilled the same criteria as those in the previous study described above (mean age at the time of hospitalization: 65 ± 10 years old, 36 cerebral infarction, 22 cerebral hemorrhage). Subjects were randomly allocated to 2 groups, the BL-rTMS group (27 subjects) and the LF-rTMS group (31 subjects). The period until the start of intervention was set at within 15 days after onset of symptoms (mean 9.7 ± 3.3 days), and thus was shorter than in the previous study. In all subjects one stimulation session was conducted each day for 5 consecutive days as described below. During these 5 days before and after intervention changes in the Brunnstrom Recovery Stage (BRS) of the upper limb and hand-finger, GP, and TAP were compared between the two groups.

2) Application of rTMS

Stimulation site and intensity were set in the same way as in Study 1. In the HF-rTMS group 10-Hz rTMS trains were applied for 10 seconds to the stimulation site on the lesional side followed by a pause of 50 seconds, and this was repeated 10 times. In the BL-rTMS group rTMS was conducted by applying 1-Hz rTMS trains for 10 minutes to the stimulation site on the nonlesional side, followed by 10-Hz rTMS trains that were applied for 10 seconds to the stimulation site on the lesional side, and 1-Hz rTMS trains that were applied for 50 seconds to the stimulation site on the nonlesional side, and this was repeated 10 times alternately.

3) Results

Prior to intervention there were no differences between the two groups regarding the clinical characteristics of the patients, stroke severity, or severity of paralysis. No adverse events were observed in any of the patients who participated in this study,

and the study protocol could be completed. During the 5 days of intervention, both in the BL-rTMS group and the HF-rTMS group a significant improvement in the BRS of the upper limb and hand-finger, GP, and TAP was observed (Table 6.2). Although increases in GP and TAP tended to be higher in the BL-rTMS group, no significant differences were observed. However, the amount of improvement of paralysis was more pronounced in the BL-rTMS group, namely, the amount of improvement in BRS of the upper limb was 1.4 ± 0.9 in the BL-rTMS group compared to 0.7 ± 0.7 in the HF-rTMS group, and the amount of improvement in BRS of the hand-finger was 1.4 ± 0.8 in the BL-rTMS group compared to 0.7 ± 0.7 in the HF-rTMS group, and thus in either case a more significant improvement was observed in the BL-rTMS group than in the HF-rTMS group (Fig. 6.4).

Interpretation of Our Study Results

This series of studies demonstrated that rTMS is also effective for the treatment of upper extremity paralysis in the acute phase of stroke, that in particular HF-rTMS is highly effective, and that through BL-rTMS, namely, the simultaneous conduct of HF-rTMS and LF-rTMS, even better results can be expected.

As noted, different from the chronic phase of stroke, spontaneous recovery is an important factor in acute stroke, and for this very reason it is necessary to set up a control group in the study design. We know from experience that a very large number of patients "have the feeling" that their condition improved even if only a coil was placed on their head. It is also conceivable that it actually affects the treatment outcome, and therefore it is desirable to conduct sham stimulation in the control group. Taking this into consideration, we conducted RCT in the first study (Study 1) in all three groups, namely, in the LF-rTMS, HF-rTMS, and sham stimulation group. In Study 2 no sham group was set up, and therefore this was only a pilot study that arose based on the results of Study 1. However, the criteria for participating in this study and the conditions for conducting HF-rTMS were the same as in Study 1.

The rationale for applying LF-rTMS in the treatment of upper extremity paralysis in the chronic phase of stroke is the overactivity of the nonlesional hemisphere, and the enhanced inhibition of the lesional hemisphere that is caused by unbalances that result from IHI [18]. This is the greatest problem that rTMS procedures must be determined distinctively for acute and chronic stroke. In short, the crucial question is when this imbalance in brain activity will occur. In the study by Marshall et al., in which functional MRI (fMRI) was used, it was shown that although brain activity of the nonlesional side was not notably enhanced in the acute phase after stroke, it was significantly enhanced after several months [19]. If that is the case, then one might not be able to expect that in acute stroke a decrease in the activity of the nonlesional hemisphere that is achieved by LF-rTMS will result in the appropriate release of the inhibited lesional hemisphere. One could also say that the results of the first study

Table 6.2 Changes in upper limb function before and after performing rTMS in Study 2

	BL-rTMS				HF-rTMS			
	Pre-intervention	Post-intervention	Change in the value	statistics	Pre-intervention	Post-intervention	Change in the value	Statistics
BRS of upper limb	2.9 (1.4)	4.3 (1.5)	1.4 (0.9)	<0.01	2.8 (1.4)	3.5 (1.5)	0.7 (0.7)	<0.01
BRS of hand-fingers	3.0 (1.6)	4.4 (1.6)	1.4 (0.8)	<0.01	2.6 (1.5)	3.3 (1.6)	0.7 (0.7)	<0.01
Grip strength, kg	4.8 (7.6)	8.4 (9.5)	3.6 (3.6)	<0.01	3.1 (5.7)	5.7 (8.2)	2.6 (3.7)	<0.01
Tapping frequency, times/30 seconds	23.6 (24.6)	36.5 (27.0)	12.9 (9.9)	<0.01	18.4 (25.0)	28.3 (30.1)	9.9 (10.7)	<0.01

BRS Brunnstrom recovery stage

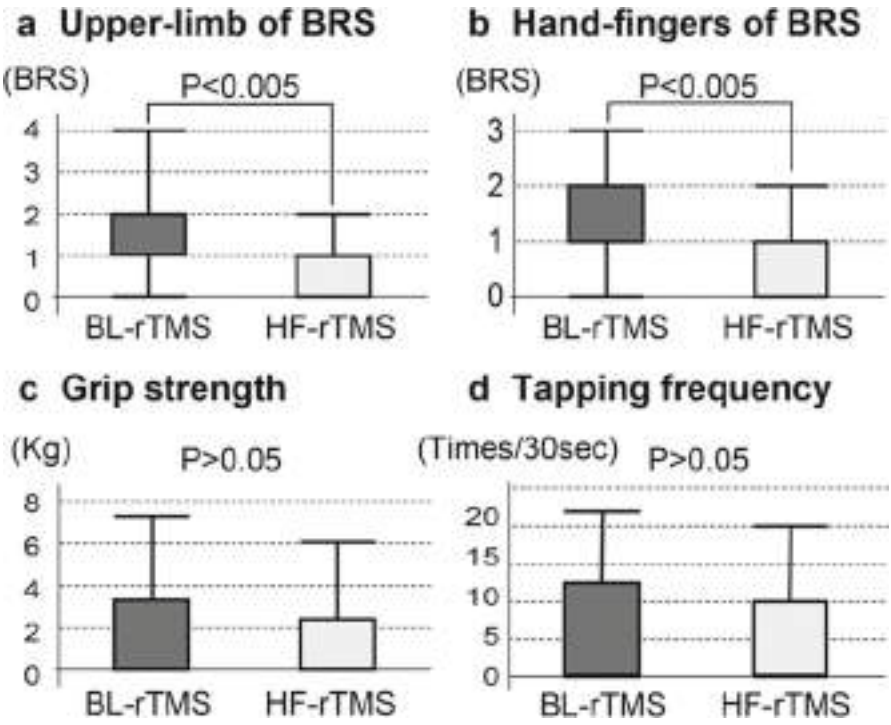

Fig. 6.4 When conducting rTMS intervention for a period of 5 days, significantly larger changes in the BRS of the upper limb and hand-finger were observed in the BL-rTMS group than in the HF-rTMS group. However, no differences in grip strength and tapping frequency were observed between the two groups

indirectly support that there is not much overactivity of the nonlesional hemisphere during the acute stage.

We think that as long as patients cannot be treated in an environment where functional brain imaging tests such as fMRI can be conducted for assessing individual brain activity, at present the most appropriate treatment method is BL-rTMS, which was conducted in the second study. Presumably, brain activity changes over time in various ways depending among other things on the size and site of the lesion, and the age of the patient. However, when applying BL-rTMS it is possible to take a direct approach with which both hemispheres can be treated simultaneously, regardless of the state of balance in the activity levels of the lesional and nonlesional hemisphere. The simultaneous application of two types of stimulation is expected to have a synergetic effect on both sides of the brain that is mediated by the IHI. This method has already been reported also to be used for the treatment of upper extremity paralysis in the chronic phase of stroke, and has been shown to be more effective than unilateral stimulation [20]. If there are any problems regarding BL-rTMS then these are the stimulation intensity and the number of stimuli. Moreover, obviously it is assumed that the unilateral application of HF-rTMS or LF-rTMS will also

increase the risk of epileptic seizures. However, similar to previous reports on the application of BL-rTMS in the chronic phase of stroke, when we used the study protocol for the treatment of acute stroke not a single patient dropped out from the study, and no side effects or adverse effects were observed. The optimal number of stimuli and the limit of its application are issues that are related to rTMS in general and require further verification over a longer period of time.

In addition, an important difference between the acute and the chronic phase of stroke is the plasticity of the brain. Gao et al. reported that in an intervention study, in which they conducted rTMS in acute stroke in a rat model of cerebral infarction, they could prevent the progression of lesions more significantly in the group in which HF-rTMS was conducted than in the group in which sham stimulation was conducted [21]. This suggests that HF-rTMS exerts effects that prevent the death of neurons. At this stage it is not clear whether LF-rTMS has the same effect; however, when considering that according to the Hebbian Learning Rule the firing rate of neurons affects the number of synaptic connections, then it is conceivable that direct stimulatory stimulation of the lesional cortex can be expected to be more effective than the reduction of excessive inhibition that is mediated by the IHI. We think that at present, from the viewpoint of brain plasticity as well, in many patients rTMS in acute stroke would be more effective, if it were conducted on the basis of HF-rTMS that is applied to the lesional hemisphere.

Future Challenges of rTMS for Acute Stroke

Although there are reports that rTMS is applied not only for upper extremity paralysis in the chronic phase of stroke but also for various symptoms such as paralysis of the lower extremity, alogia, other higher brain dysfunctions, dysphagia, and ataxia, there are still only very few reports on the application of rTMS in acute stroke, and the fields of application are only limited. Taking together the findings that were made to date, there are many cases in which methods that are effective in the chronic phase of stroke are also effective in acute stroke without having to be changed. We therefore think that after a treatment method was confirmed to be effective and safe in the chronic phase of stroke, it is possible to immediately move on to studies that apply this method in acute stroke. In fact, a future challenge is to search for a strategy that is effective in acute stroke.

Regarding this search for an effective treatment strategy, from a macroviewpoint it will be particularly important to find out “what should be done, and when should it be done?” Originally we did not think that the conduct of rTMS intervention for the treatment of upper extremity paralysis in acute stroke should be accorded so much importance. However, different from rTMS in the chronic phase of stroke, it is especially important to follow an order of priority when applying rTMS in acute stroke. Having an effective weapon such as rTMS it makes no sense to use up this method for a weak enemy, or to lose against a strong enemy that might have been defeated if one had applied rTMS. Currently, rTMS is still at the stage where it

needs to be confirmed for which kind of cerebral symptoms it is effective. However, at the same time the question in which order rTMS should be applied is also of great importance in clinical practice.

Also from a microviewpoint there is still a mountain of problems; however, the determination of the optimal stimulation site, which is also still an unresolved issue of rTMS in the chronic phase of stroke, is particularly important because it is highly likely that it changes over time in acute stroke. At present the most widely used method for determining stimulation sites for the treatment of motor paralysis, regardless of whether it is for acute stroke or the chronic phase of stroke, is the detection of motor response by single-pulse TMS. However, it will be necessary to identify stimulation sites in accordance with, for instance, Penfield's homunculus or the Brodmann areas, and also to compare the effectiveness of the stimulation of "anatomically correct" sites such as stimulation sites that were determined based on functional brain imaging such as fMRI. A navigation system is required when conducting rTMS at such sites. With such a system it should be possible to conduct exactly localized stimulation by entering the targeted brain MRI data into a computer and through three-dimensional analysis of the direction of the coil and head.

Conclusions

Although it is tempting to draw attention to the effectiveness of rTMS as a new therapeutic intervention measure in acute stroke, the information that is available to date is still not sufficient. The most important point when applying rTMS in acute stroke is that the improvement that is achieved by rTMS intervention may not be inferior to the degree of recovery that would have been achieved with conventional intervention alone. It is necessary to carefully proceed with research being aware of the fact that the duration of the acute stage of stroke is limited and cannot be turned back.

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Chapter 7
Case Presentation (Including TMS Device Handling Instructions)

Handling the TMS Device (MagPro)

Not many different types of TMS device are widely used in Japan. The MagPro manufactured by MagVenture (headquartered in Denmark) and the Magstim Rapid manufactured by Magstim (headquartered in the UK) seem to be the mainstream products (Fig. 7.1).

This section briefly describes how to actually handle MagVenture's MagPro, which is the device we use. When applying rTMS therapeutically, it is advisable to prepare a wheelchair with a head-holder cushion as shown in Fig. 7.2, as it is important to fix the position of the patient's head. It also goes without saying that it is essential to obtain the approval of the ethics committee of each institution when carrying out rTMS (rTMS is not approved for therapeutic purpose).

Starting Up the Device and Preparing the Patient

(i) After confirming that the patient is not in poor physical condition, seat the patient in a wheelchair as shown in Fig. 7.3. Then, tell the patient to relax, keeping his or her eyes closed (leaning against the wheelchair, with the back of his or her head in close contact with the head-holding cushion). Have the patient rest both hands and upper limbs on top of his or her thighs. Ensure the patient is not wearing spectacles or a wristwatch or carrying a mobile phone or cards that may be affected by a magnetic force when performing rTMS.

(ii) After connecting the figure-8 coil (manufactured by MagVenture) to the TMS device main unit, turn on the switch at the rear of the main unit. The LCD panel will start up after 20–30 seconds (Fig. 7.4).

(iii) If a cooler system is also fitted, ensure that the power supply to the system is also plugged in (if a cooler system is fitted, the coil surface is less likely to overheat, enabling continuous rTMS).

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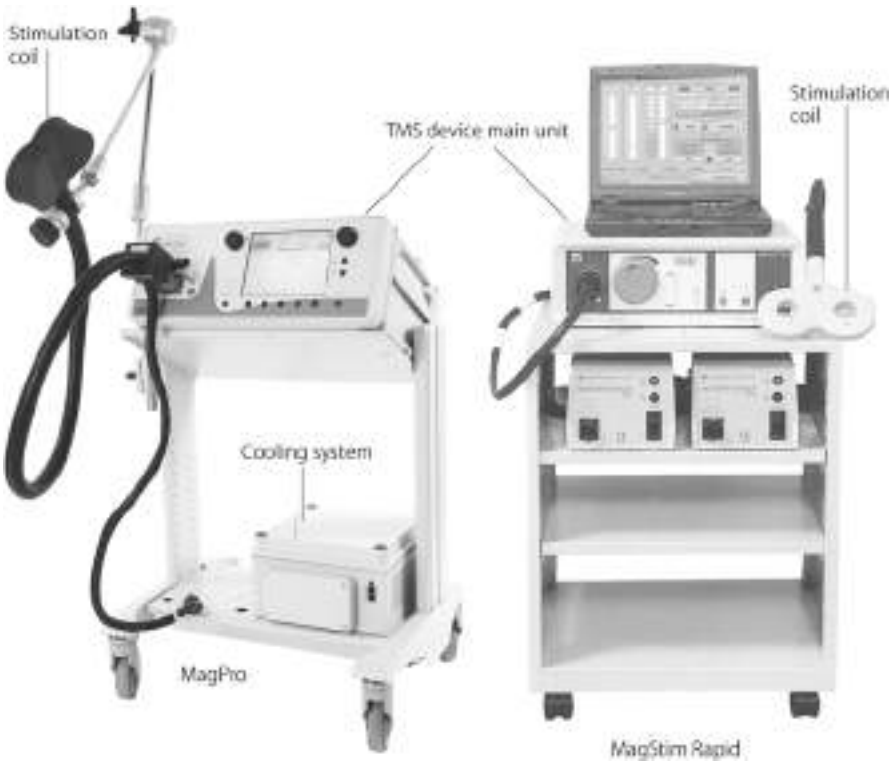

Fig. 7.1 Typical TMS device. The MagPro R30 shown in the photo also has a cooling system to prevent coil overheating

Determining the Stimulation Site and Intensity

(i) Insert the electromyography (EMG) line into the rear of the TMS device (the other end of the line is connected to the electrodes placed on the skin). Then, press the button under "Configure" displayed in the LCD panel (Fig. 7.4), and press the button under "MEP" (motor invoked potential) on the LCD panel, which is displayed next. As a result, the panel is now in EMG mode. Then, by moving the cursor up and down, set "Time Base" in EMG mode to "5 ms/div" (1 memory will be 5 ms and MEP occurring 20–25 ms after stimulation will be shown in the middle of the screen) and "Sensitivity" to "100 or 200 μV/div" (Fig. 7.5). Then, when you press button 1 (Fig. 7.4), "Status" at the top left of the panel will change from "Disabled (Red Screen)" to "Enabled (Green Screen)" and magnetic stimulation is enabled.

(ii) If applying rTMS in poststroke patients with upper limb hemiparesis, it is usual to apply rTMS in the hand and finger area of the primary motor cortex.

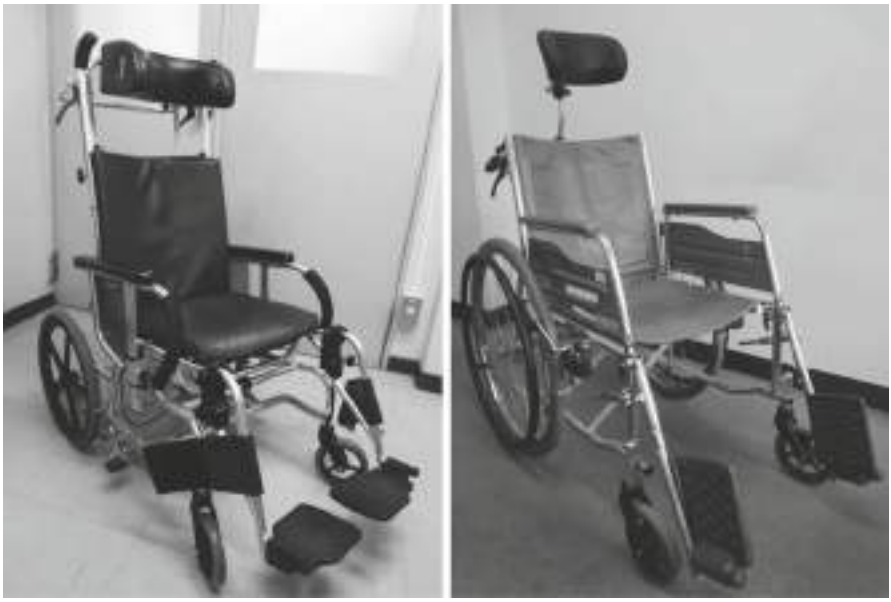

Fig. 7.2 Wheelchair with head-holder cushion. Designed so that the position of the head can be fixed during rTMS procedure

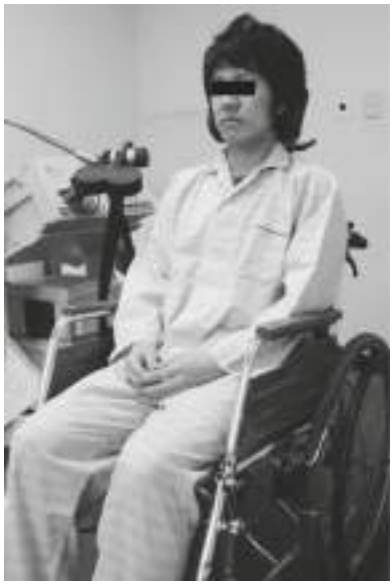

Fig. 7.3 Posture of patient during rTMS delivery. Sitting, relaxed with eyes closed

Fig. 7.4 LCD panel. All operations including confirmation of MEP waveform and setting of rTMS stimulation modality can be performed on this screen

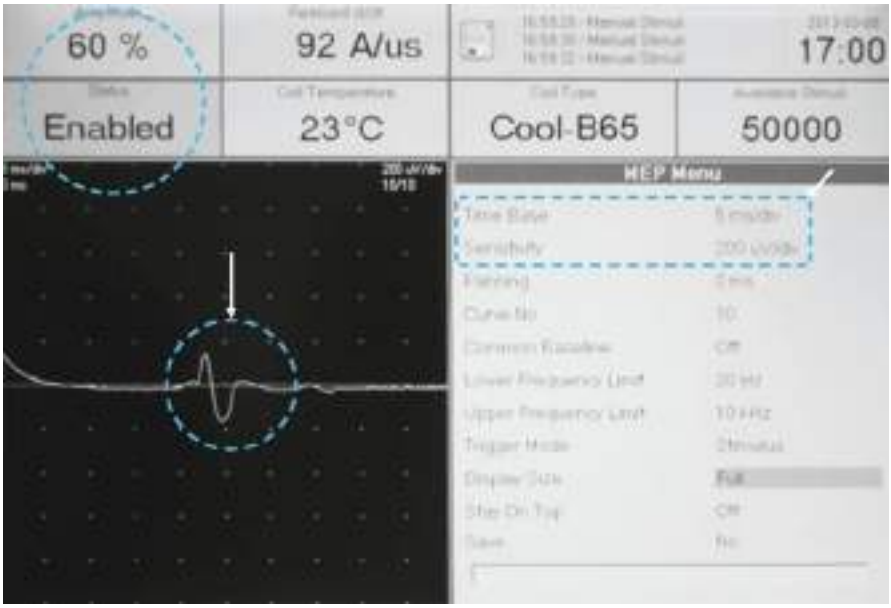

Fig. 7.5 MEP waveform. By applying single pulse magnetic stimulation to the primary motor cortex, it is possible to induce MEP from the muscles at the stimulation site

Our practice is to take the primary motor cortex corresponding to the first dorsal interosseous muscle (FDI muscle) of the nonparalyzed upper limb in the nonlesional hemisphere as the stimulation site for low-frequency rTMS. Therefore, when determining the stimulation site for upper limb hemiparesis, first attach the electrodes of the surface EMG to the FDI muscle of the nonparalyzed upper limb as shown in Fig. 7.6 [In the figure, the red (b) and black (c) plugs are the measurement electrodes, and the green (a) plug is the earth.]

(iii) The person delivering rTMS places the figure-8 coil near the primary motor cortex on the unaffected hemisphere, presses button 2 (Fig. 7.4) or the button for single pulse stimulation next to the coil, and, while repeating magnetic stimulation in single pulses, gradually increases the stimulation intensity (Fig. 7.7). Stimulation intensity can be increased by turning dial 1 (Fig. 7.4) clockwise [stimulation intensity is shown in percent (%) as "Amplitude"]. In the case of MagPro, it is better to start from an intensity of approximately 20 % and, after applying around approximately 3–4 pulses of stimulation each time, increasing stimulation intensity in increments of 3–5 %. Then, detect the site at which movement of the nonparalyzed index finger can be induced most noticeably, moving the site of application of the figure-8 coil bit by bit. It is better to visually confirm movement of the index finger initially and then to check that MEP of the FDI muscle of the nonparalyzed upper limb is being induced on the EMG (Fig. 7.5).

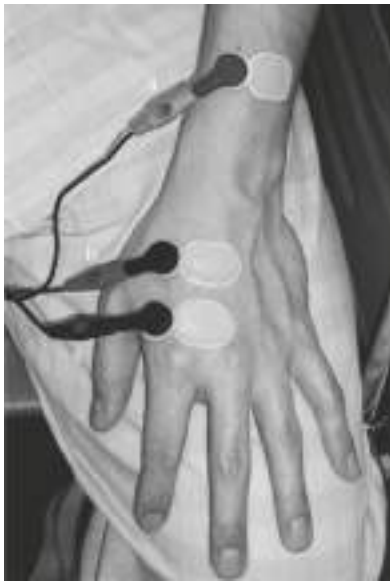

Fig. 7.6 Attachment of the EMG electrodes. Electrodes are often attached to the FDI muscle, but can also be attached to the abductor pollicis muscle

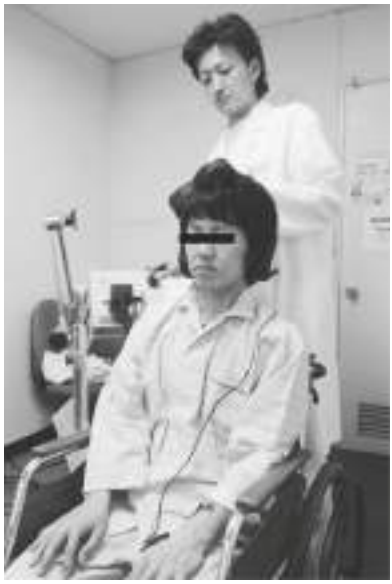

Fig. 7.7 Confirmation of the stimulation site. Detect the site at which MEP can be induced most noticeably, gradually increasing the stimulation intensity by turning the dial of the main unit with your right hand

Fig. 7.8 Marking of stimulation site. Mark the stimulation site to prevent displacement of the stimulation site in subsequent rTMS sessions

(iv) Once the site at which MEP can be induced most noticeably is determined, measure the resting motor threshold, which is defined as "the minimum stimulation intensity at which MEP with amplitude of 50 μV or more can be induced with a probability of 50 % of more." Then, take 90 % of this intensity as the rTMS stimulation intensity (e.g., if the resting motor threshold is 60 %, the stimulation intensity used in therapy will be 54 %. Then, movement of the nonparalyzed hand should not occur during the rTMS treatment).

(v) Once the stimulation site is determined, upon obtaining the patient's approval, mark the stimulation site with a marker pen as shown in Fig. 7.8 to ensure that the site does not move in subsequent rTMS sessions. While it is, of course, advisable to confirm the stimulation site by inducing MEP each time rTMS is

Fig. 7.9 Example of marked stimulation site. It is advisable to draw a cross with a marker pen

delivered, marking the approximate stimulation site in this way will facilitate determination of the stimulation site on subsequent occasions. Figure 7.9 shows an example in which the marked site is seen from directly above. The hand and finger area of the primary motor cortex is often situated approximately 2–5 finger breadths away from and slightly in front of Cz (vertex) based on the International 10–20 Method for EEG.

(vi) If movement of the hand of the nonparalyzed upper limb is not induced even after the stimulation intensity is increased to approximately 90 %, it is possible that the coil is improperly positioned, but, in some patients, movement cannot be induced even when stimulation intensity is 100 %. This is presumably due to the thickness of the skull. In such cases, it is better to lower the motor threshold and create a situation in which movement of the hand will be induced more easily by extending and elevating the nonparalyzed upper limb and dorsiflexing the wrist. This will make it more difficult to reliably set the exact stimulation intensity but will probably make it easier to determine the stimulation site.

(vii) If applying high-frequency rTMS to the primary motor cortex in the unaffected hemisphere in poststroke patients with paralyzed upper limb, first attach the EMG to the FDI muscle of the paralyzed upper limb. Then, detect the site at which movement of the paralyzed FDI muscle can be induced and the site at which MEP of the paralyzed FDI muscle can be induced by stimulating the primary motor cortex of the affected hemisphere. However, it is not uncommon for it to be impossible to invoke or induce movement and MEP of the paralyzed FDI muscle even at maximum stimulation intensity. In such cases, it is probably better to first detect the site at which movement and MEP of the nonparalyzed FDI muscle can be invoked or induced and then determine the corresponding site as the rTMS application site.

(viii) The right or left inferior frontal gyrus of frontal lobe is reportedly often selected as the rTMS application site in poststroke aphasic patients. While it is normally advisable to use an MRI navigation system to determine the position of the inferior frontal gyrus, only a limited number of institutions have such a system. However, areas F7 and F8 according to the International 10–20

Method have been confirmed to correspond to the left and right inferior frontal gyrus respectively. Therefore, therapeutic rTMS in aphasic patients (especially patients with motor aphasia) is probably actually applied in this F7 area or F8 area based on the International 10–20 Method. The stimulation intensity of rTMS in patients with aphasia is usually determined by measuring the resting motor threshold of the nonparalyzed upper limb FDI muscle in the same way as for upper limb hemiparesis and setting intensity at about 90 % of this.

Application of rTMS

(i) If applying TMS in the form of therapeutic rTMS, first set the "Waveform" and "Timing Menu" (Fig. 7.10). The nature of rTMS stimulation (stimulation modality) will be determined based mainly on the Timing Menu.

(ii) With the Main Menu displayed on the right side of the panel, move the cursor to Waveform and select "Biphasic" (not Monophasic) (Fig. 7.11). Since the magnetic energy released from the coil is greater with "biphasic" than with "monophasic," it is better to use "biphasic" if using rTMS therapeutically.

(iii) When you press the button under "Main" on the LCD panel (Fig. 7.4), the word "Timing" will appear, and the "Timing Menu" will be displayed on the right side of the panel. Then set the stimulation modality. "Rep Rate (repetitive rate)" shown here denotes frequency (pps = pulses per second), and "Pulses in Train" denotes the number of pulses delivered in one stimulation train. "Number of Trains" shows how many stimulation trains are to be administered overall, and "Inter Train Interval" shows the interval between trains.

Fig. 7.10 Timing Menu display. Stimulation modality (nature of stimulation) is displayed in the form of Timing Menu

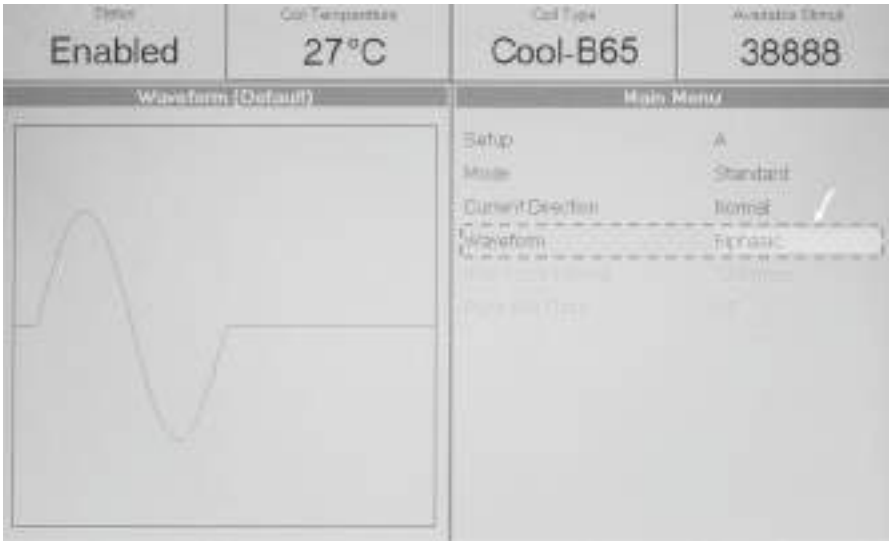

Fig. 7.11 Selection of stimulation waveform. Biphasic waveform is advisable if using as rTMS for therapeutic purposes

Fig. 7.12 Commonly used settings for low-frequency and high-frequency rTMS. (**a**) Setting for low-frequency rTMS (1 Hz). (**b**) Setting for high-frequency rTMS (10 Hz)

(iv) If delivering low-frequency (1 Hz) rTMS for 20 minutes, set as shown in Fig. 7.12a. First, set Rep Rate as 1 pps (1 Hz) and Pulses in Train as 600. This means that 600 pulses at 1 Hz will be delivered per train; in other words, 10 minutes of 1 Hz stimulation will be delivered. If you then set the Inter Train Interval at 1 second and the Number of Trains at 2, this means in effect

that 2 stimulation trains (in other words, 600 pulses × 2 trains = 1200 pulses) will be delivered continuously, lasting 20 minutes.

(v) To deliver high-frequency (10 Hz) rTMS using 10 second pulses at 50 second intervals for 20 minutes, set as shown in Fig. 7.12b. First, set the Rep Rate as 10 pps (10 Hz) and Pulses in Train as 100 (100 pulses at 10 Hz per train = 10 seconds) and the Inter Train Interval at 50 seconds. This means that one train lasts a total of 1 minute comprised of 10 seconds of 10 Hz stimulation and an interval of 50 seconds. Moreover if you set the Number of Trains as 20, this means that this stimulation train will be repeated 20 times, lasting 20 minutes. In other words, this means that 100 pulses × 20 trains = 2000 pulses will be delivered.

(vi) Once you have finished setting stimulation modality, use the fixed arm fitted to the TMS main unit to firmly fix the stimulation coil to the marked stimulation site as shown in Fig. 7.13. Next, press button 1 (Fig. 7.4) to turn "Status" at the top left of the panel to "Enabled" (Green). Then, press the button below "Start" on the LCD panel (Fig. 7.4). When you do this, the set stimulation will start immediately.

(vii) During rTMS delivery, you will be accompanied by a doctor, as a general rule, in case an adverse effect or adverse event occurs. rTMS is painless, and patients we have actually treated have never complained about clearly localized head pain. However, when the stimulation intensity increases, the muscle surrounding the stimulation site is directly stimulated, and muscle contraction of the temporal region, palpebral part, buccal region, etc. may occur at the same time as the stimulation. In addition, in patients with noticeable body

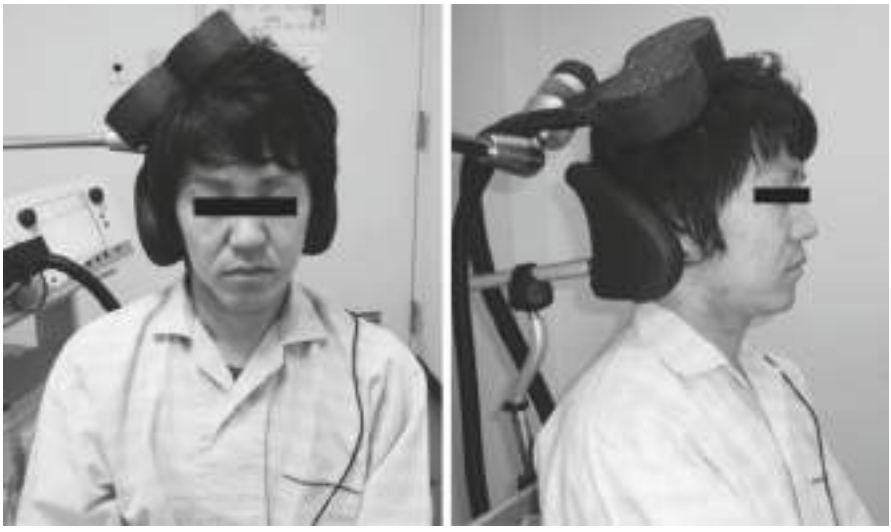

Fig. 7.13 Actual rTMS delivery. The stimulation coil is held by a rigid arm

movements (patients who find it difficult to maintain the same posture), since it is not uncommon for the coil to become displaced, ensure that stimulation is applied to the right site by checking the position of the coil as required and correcting the position of the coil if necessary.

Case 1

A 75-year-old male patient for whom importance was attached to ADL guidance in occupational therapy as part of NEURO-15 and an improvement of motor function in a paralyzed upper limb was linked to ADL.

Medical History and Background

In October 2010 (at the age of 74), the right-handed patient was taken to a nearby hospital by ambulance after weakness occurred on the left side of his body. He was diagnosed with right putaminal hemorrhage and admitted to hospital as an emergency. After being treated with conservative therapy, he was transferred to a convalescent rehabilitation hospital in December 2010. For approximately 3 months after admission, the patient underwent rehabilitation, but left upper limb hemiparesis persisted, and it was difficult for the patient to use his left upper limb practically. In February 2012, the patient was admitted to our hospital for treatment of the left upper limb hemiparesis. Before being admitted to the hospital, the patient went to day care four times a week. The patient lived with his wife and other family members and had worked as a carpenter for approximately 60 years before the onset of symptoms.

Pretreatment Physical Findings

[General physical findings] Height 165 cm, weight 50 kg

[Consciousness] Clear

[Higher brain function] Mini Mental State Examination (MMSE) 27/30 points. Otherwise, satisfactory

[Motor system] Evidence of left upper limb hemiparesis. Compensatory movement with trunk lateral flexion/rotation was observed during flexion of the shoulder joint, and poor dynamic stability of proximal portion was found. Brunnstrom recovery stage (BRS) was equal to stage III for left upper limb and stage IV for left hand and finger. In the flexor muscles of the left upper limb, a clear increase in muscle tone was found, and an increase in the biceps tendon and brachioradialis reflex of the left upper limb was also found.

[Sensory system] Superficial sensation and deep sensation of the left upper limb are both at a moderately dull level.
[Standing and walking] Patient is stable when standing and can move by walking independently within his own home. However, outside, the patient uses a T-shaped cane and needs monitoring. He does not use an orthosis.
[ADL] The patient is independent except when taking a bath. He hardly uses his left upper limb in ADL. When he goes out, he goes with his wife.

Evaluation Results

The results of each evaluation performed from the time of admission to 4 weeks after discharge are as shown in Table 7.1.

Pretreatment Image Findings

A high-intensity area indicating old cerebral hemorrhage in the right putamen was found in head MRI (T2-weighted image).

Table 7.1 Evaluation results

Evaluation method/items		At admission	At discharge	4 weeks after discharge
BRS[a]	Left upper limb	III	III	III
	Left hand and finger	IV	IV	IV
MAS[b]	Left elbow flexor muscles	1	1	1
	Left wrist flexors	1	1	1
	Left finger flexor muscles	1	1	1
ROM[c] (passive)	Left shoulder joint flexion	90	100	140
	Left shoulder joint abduction	90	100	140
FMA (upper limb)[d]	Overall score	43	47	16
WMFT[e]	15 tasks perf. time (seconds)	172.83	83.99	82.38
	FAS[f]	45	53	50
10-second test (grip and release) (times)		3	6	6

[a]BRS (Brunnstrom recovery stage)
[b]MAS (modified Ashworth scale)
[c]ROM (range of motion)
[d]FMA (Fugl-Meyer assessment)
[e]WMFT (Wolf motor function test)
[f]FAS (functional ability scale)

Patient's Needs, Treatment Goal, and Treatment Plan

The need of the patient was for "the left arm and hand and finger to be completely returned to normal." However, there was a severe degree of upper limb hemiparesis, and practical use was judged difficult. We, therefore, focused on the hand and finger with comparatively good function and, upon consultation with the patient himself, set a concrete treatment goal of "being able to hold a plastic bottle or can." In addition, since the left upper limb was hardly used in ADL, we added the objective of "increasing opportunities to use the left upper limb in ADL." Based on this, we adopted the hospital treatment plan of providing OT focusing on training to improve the dynamic stability of the left shoulder joint and left hand and finger holding training, while delivering rTMS to the hand and finger area of the primary motor cortex in the nonlesional hemisphere on a daily basis.

Content of Rehabilitation Program

(i) Application of low-frequency rTMS to the hand and finger area of the primary motor cortex in the left (nonlesional) hemisphere (20 minutes twice daily)
(ii) Range of motion (ROM) training aimed at increasing the ROM of the left shoulder joint
(iii) Stretching aimed at reducing the muscle tone of the left shoulder joint, elbow joint, wrist, and finger joints
(iv) Holding training and pinching training using various objects to improve left hand dexterity
(v) Facilitation training aimed at increasing voluntary movement of the triceps brachii muscle, extensor carpi radialis brevis muscle, extensor carpi ulnaris muscle, and extensor digitorum muscle of the upper limb using EMS (electric muscle stimulation)
(vi) Facilitation training for shoulder muscles aimed at increasing dynamic stability of the left upper limb proximal portion
(vii) Guidance on actively using the left upper limb in ADL in hospital (eating, getting changed, washing face, washing hair, etc.)
(viii) Self-exercise to improve function of left upper limb for 2 hours daily, guidance focusing on object holding and manipulation training

Course

From the day following admission to hospital, we delivered rehabilitation focusing on training to improve the dynamic stability of the left upper limb proximal portion and left hand holding training. We also provided due guidance on using the left upper limb

in ADL. As a result, from around the fifth day in hospital, extension of the left elbow joint and palmar abduction using the left abductor pollicis muscle became possible, and the patient himself also began to say that he has more opportunities to use his left hand more than before. At discharge, shoulder joint ROM was also greater, and the patient could grip a plastic bottle or can and raise it to his mouth. As shown in Table 7.1, in evaluation, a noticeable improvement in WMFT was found. The patient himself also fully understood the need to complete the rehabilitation program and self-exercise and worked hard throughout. After discharge, he reportedly completed the independent training at home almost every day and, 4 weeks after discharge, the improvement in the motor function attained at discharge had been maintained.

Discussion

The patient had moderate hemiparesis of the left upper limb and left hand and finger and hardly used the left upper limb in ADL. We, therefore, focused on the hand and finger with comparatively good function and adopted the approach of focusing on improvement of hand function with the aim of making the left hand an assistive hand. Since the restricted ROM of the shoulder joint was also obstructing upper limb manipulation, we took the approach of improving the dynamic stability of the upper limb proximal portion in addition to improving the ROM of the shoulder joint. We believe that our approach of providing ADL guidance as required combined with improvement of function helped to increase frequency of use of the left upper limb and left hand in ADL. The patient himself commented that "I gradually became able to use my left hand in life on the ward," and our approach may also have helped to increase awareness of using the left upper limb in ADL and to increase training motivation.

Patient's Impressions

> After receiving the rTMS treatment, I am able to use my left hand, which had previously hardly used at all, and to understand how to use it. Since I received not only functional training but also guidance on how to use my left hand in daily life from the day after my admission, I was able to practice this gradually while in hospital and felt that I used my left hand more and more frequently day by day.

Conclusion

Alongside improvement in function, we provided the patient with guidance on using his left upper limb, which was previously unusable, in ADL and combined intensive OT with rTMS. As a result, the holding function of the hand and frequency of use

of the left upper limb in ADL showed improvement both subjectively and objectively. This suggested that the approach of including ADL guidance using the paralyzed side in addition to rTMS treatment and functional training is a useful therapeutic intervention.

Case 2

A 65-year-old male patient whose handwriting movements became independent and who was able to return to work as a result of continuous rTMS on an outpatient basis after completion of NEURO-15.

Medical History and Background

In February 2010 (at the age of 64), the right-handed patient noticed heaviness in the head, difficulty articulating, and weakness on the right side of the body and, when examined at a nearby hospital, was diagnosed with cerebral infarction, urgently admitted, and underwent emergency treatment at the hospital. He was later transferred to another hospital for rehabilitation purposes, and although he was discharged after 5 months in hospital, he still had hemiparesis of the right upper and lower limbs. It was, therefore, judged difficult for him to return to work, and he retired for a time. However, the patient was admitted to our department in November 2010 because he wished to undergo specific rehabilitation for the right hemiplegia with the aim of returning to work. The patient had a history of hypertension and was taking antihypertension drugs, etc. He lived with his wife and second daughter. He previously commuted to his company by train. His hobby was golf, but he was no longer playing and spent his days helping with the housework and going for walks.

Pretreatment Physical Findings

[General physical findings] Height 165 cm, weight 65 kg. In a standing position, the center of gravity was offset to the nonparalyzed side, and the upper limb on the paralyzed side showed slight inner rotation of the shoulder joint and slight flexion of the elbow joint.

[Consciousness] Clear

[Higher brain function] The patient himself was aware of his difficulty articulating but had no problem communicating. The higher brain function screening test showed no other abnormal findings.

[Cranial nervous system] Evidence of dysphagia and facial paralysis on the right side

[Motor system] Moderate hemiplegia was found in the right upper limb. BRS on the paralyzed side was equal to stage IV for upper limb and stage IV for hand and finger, there were severe contractions of the flexor muscles, and an increase in reflexes was also observed.

[Sensory system] Superficial sensation and deep sensation are both normal. There is no sign of pain, sense of numbness, etc. on the paralyzed side.

[Standing and walking] The patient can walk independently indoors using an ankle-foot orthosis. However, outdoors, he uses a stick as he stumbles and is unstable. An increase in flexor muscle spasticity of the paralyzed upper limb was observed when walking.

[ADL] While the patient could perform basic movements and ADLs independently, frequency of use of the paralyzed upper limb was low, and use was restricted to certain actions such as wringing a cloth or towel, tearing off toilet paper, or fastening a belt. Although the patient had attempted performing chopstick and writing movements with the paralyzed upper limb, increased spasticity of the flexor muscles of the entire upper limb from the shoulder girdle through the hand made this virtually impossible.

Evaluation Results

The results of each evaluation performed from the time of admission to 8 weeks after discharge are as shown in Table 7.2.

Pretreatment Image Findings

A low-density area suggesting old infarction lesions in the left basilar pons was found in plain head CT.

Table 7.2 Evaluation results (Case 2)

Evaluation method/evaluation items		At admission	At discharge	8 weeks after discharge
MAS	Elbow flexor muscles	1^+	1	1
	Wrist flexor muscles	1^+	1	1
	Finger flexor muscles	1^+	0	0
FMA (upper limb)	Overall score	55	57	–
WMFT	15 tasks perf. time (seconds)	87.92	60.02	50.98
STEF[a]		27	45	–

[a]STEF (simple test for evaluating hand function)

Patient's Needs, Treatment Goal, and Treatment Plan

The needs of the patient were that he wanted to write with his right hand and wanted to eat holding chopsticks in his right hand. However, upon consultation with the patient, we set the treatment goals of being able to write his name with a pencil and being able to eat with a self-help device chopstick, since, in view of the existing status of isolated movements of the upper limb/hand and finger, work for a sustained period of time would be difficult and use of a self-help device was considered necessary. Based on this, we adopted the hospital treatment plan of delivering functional training aimed at facilitating isolated movements of the paralyzed upper limb proximal portion and hand and finger, and providing OT focusing on task-oriented ADL training such as handwriting and chopstick movements, while delivering low-frequency rTMS for 40 minutes on a daily basis throughout hospital stay.

Content of Rehabilitation Program

(i) Application of low-frequency (1 Hz) rTMS to the hand and finger area of the primary motor cortex in the right (nonlesional) hemisphere (40 minutes once daily)
(ii) Static stretch aimed at reducing muscle tone of flexor muscles from shoulder joint through finger joints (for approximately 1–2 minutes at the end of each movement session in individual OT; guidance to do self-stretching at the end of each task in self-exercise)
(iii) Repeated performance of single joint movements from shoulder joint through wrist joint (while applying resistance according to strength of patient's own muscle force output)
(iv) Repeated performance of multijoint movements from shoulder joint through wrist joint (especially aiming to achieve eccentric contraction of agonists during movements)
(v) Facilitation of isolated movements of hand and finger using objects (with awareness of grading of hand and finger control, from task of fixing object using chuck pinch to extending index finger only with object fixed using chuck pinch)
(vi) Self-exercise done focusing on program aimed at improving isolated movements (gross motor skills) and exercise endurance

Course

When we provided rehabilitation aimed at reducing hypertonia of the hand and finger for 3 days from the day of admission, a reduction in the muscle tone of the hand and finger began to be noticed from around the second day in hospital, and the

patient was able to perform hand and finger movements multiple times. The patient himself also recognized that it had become easier to move his hand and finger.

After confirming that isolated movements of the hand had been facilitated, we focused on single-joint movements and multijoint movements on the paralyzed upper limb proximal side. However, though single-joint movements were possible, when it came to multijoint movements and composite movements, increased muscle tone of the wrist flexors and biceps brachii muscle and compensatory movements such as elevation of the shoulder blade and shoulder abduction were observed. We, therefore, provided rehabilitation consisting mainly of single-joint movements, with particular focus on the eccentric contraction of muscles prone to increased muscle tone. As a result, after 1 week in hospital, increased muscle tone and excessive effort in multijoint movements and composite movements were no longer evident, and the patient himself also said that he had "got the knack of relaxing."

At discharge, he achieved the handwriting movements he had hoped for, as expressed by himself that he was able to write characters more or less the same as before his stroke, and he was also able to perform face washing and drinking movements in everyday life. However, when it came to chopstick movements, while the patient started out well, he gradually became fatigued, and eventually his fingers would no longer work. Consequently, at the behest of the patient himself, it was decided that the patient would visit the outpatient rehabilitation clinic of the hospital once a week and undergo 20 minutes of low-frequency (1 Hz) rTMS and 40 minutes of individual rehabilitation.

In the outpatient rehabilitation, we continued to facilitate isolated movements of the hand and finger and also carried out OT focusing on improving endurance of the proximal side of the paralyzed upper limb. As a result, 2 months after starting outpatient rehabilitation, the patient became able to use chopsticks to the end of a meal. After 4 months, the outpatient rehabilitation came to end, partly at the request of the patient who had returned to work and was now busy with work.

Discussion

The patient presented moderate right hemiparesis, and it was considered that, functionally, the right hand was usable as an assistive hand. However, during movement, increased muscle tone of the paralyzed upper limb flexor muscles and excessive effort caused actual movement patterns to be clumsy. As a result, the patient hardly used the paralyzed upper limb in ADL, and we believe that learned nonuse and decrease in muscle function due to nonuse occurred. When we carried out NEURO-15 to address this situation, functional improvement of the paralyzed upper limb and increased frequency of use in ADL were observed as a result of intervention during hospitalization. We were able to link this to a return to work by continuing ongoing intervention through rehabilitation on an outpatient basis.

It has been suggested that NEURO-15 is also effective in reducing the spasticity of the paralyzed upper limb, and in this patient, this spasticity-reducing effect was

indeed evident, and this may have led to the patient learning normal movements by controlling excessive effort and compensatory movements. On this occasion, the effect of NEURO-15 was most evident after 1 week in hospital, and we believe we were able to prevent an increase in spasticity and facilitate the learning of normal movements through the grading intensive OT treatment content in line with this effect.

For this patient, we continued regularly delivering rTMS treatment on an outpatient basis after completion of NEURO-15. In the case of patients like this patient who have no particular problem visiting hospital, the strategy of continuing rTMS on an outpatient basis may be useful.

In the case of this patient, we began rTMS treatment before 1 year had elapsed from onset because the time he planned to return to work was approaching. Eligibility criteria for NEURO-15 as of December 2012 state that the time from symptom onset to therapy must be at least 1 year, and previously, in almost all patients, we delivered rTMS treatment once 1 year had elapsed from onset. However, safety of staring treatment from the acute phase has also been confirmed in many papers, and, in the future, we will examine the usefulness of introduction of rTMS treatment at an earlier stage.

Patient Impressions

> I am now able to write. The fact that I am now able to write better (with my right hand) than with my left hand is like a dream. I now intend to continue practicing so I can use chopsticks a little better.

Conclusion

In this patient, we were able to achieve the objectives of chopstick and handwriting movements by carrying out NEURO-15 based on consideration of reduction of spasticity and self-control of muscle force output. Achievement of the target movements also produced motivation to achieve other ADL movements and return to work, and we were able to help the patient to achieve a more independent lifestyle.

Case 3

A 70-year-old female patient for whom further improvement in upper limb motor function on the paralyzed side was observed as a result of repeated NEURO-15.

Medical History and Background

In April 2001 (at the age of 60), the right-handed patient developed intracerebral hemorrhage (left thalamus) and was urgently admitted to a nearby hospital. She was later hospitalized in a convalescent rehabilitation hospital for approximately 6 months. Following long-term rehabilitation for right hemiparesis, her right upper limb improved to the level of an assistive hand, and she was discharged. However, the patient soon developed depression, preventing rehabilitation for right hemiparesis, and contracture of the right elbow and wrist joint became evident. She was then admitted to a psychiatric hospital for approximately 1 year for treatment of depression.

In May 2011, the patient was admitted to our hospital for the purpose of intensive rehabilitation for right upper limb hemiparesis (first time). As a result of NEURO-15, right upper limb motor function improved, and the patient regained eating movements using a chopsticks-type self-help device. Following discharge, the patient was even able to attempt horse riding, which was her hobby, while undergoing treatment such as ambulatory rehabilitation, swimming, electric therapy, and acupuncture. However, in September 2012, she was once again hospitalized in our hospital for further intensive rehabilitation for right upper limb hemiparesis (second time). The patient had a history of hypertension and hyperlipidemia and was still on medication (antithrombotics, antihypertensives, vasodilators, lipid-lowering agents, etc.). She had been working in the teaching profession until the age of 50, had then become a full-time housewife, and now lived alone.

Pretreatment Physical Findings (Second Time)

[General physical findings] Height 138 cm, weight 44 kg. Right scapula is depressed, right upper limb as a whole tends to internally rotate, and subluxation of approximately one fingerbreadth is evident. The trunk bends to the right, and there is a tendency for a round back. The neck was extended to hold the head horizontal from round back, and muscles from neck to trapezius were overstrained.

[Consciousness] Clear

[Higher brain function] No abnormal observations (Results of evaluation do not show depression.)

[Cranial nervous system] No abnormal observations

[Motor system] Right upper limb shows paresis and is at level of assistive hand. Although there is contraction of the MP joint and PIP joint of the ring finger on the right hand, hand BRS is equal to stage IV. Increased muscle tone of flexor muscles was observed in right wrist and all finger joints. Upper limb BRS is equal to stage III, and increased muscle tone was observed in flexor muscles of right elbow joint. During right upper limb manipulation, motor ataxia as a result of difficulty adjusting the muscle output force of the agonist and antagonist muscles was observed.

[Sensory system] Surface sensation and deep sensation are both slightly dull on the left side of the body and in particular very dull in the hand. Numbness was observed in the right side of the body.
[Standing and walking] Indoors, the patient walks independently, and outdoors she is independent walking with a stick.
[ADL] Although she was independent in all ADL, she was unable to do housework movements herself and asked a helper to do them. She moved around the neighborhood by electric bicycle.

Evaluation Results

The results of each evaluation performed at admission and at discharge the first and second times were as shown in Table 7.3.

Pretreatment Image Findings

Abnormal signal intensity indicating old hemorrhagic lesion was observed in the left thalamus in head MRI (T2-weighted image).

Patient's Needs, Treatment Goal, and Treatment Plan

The patient's need during the hospitalization for the first time was "to eat with chopsticks," and, at the time of discharge, she was able to achieve this activity using a chopstick-type self-help device. During the hospitalization for the second time, her need was "to ride a horse, holding the reins in here right hand and the whip in her

Table 7.3 Evaluation results (Case 3)

Evaluation method/items		First time		Second time	
		At admission	At discharge	At admission	At discharge
BRS	Right upper limb	III	IV	III	V
	Right hand finger	IV	IV	IV	IV
MAS	Wrist flexor muscles	1	0	1	0
	Finger flexor muscles	4	4	3	1^{+}
FMA (upper limb)	Overall score	45	51	50	53
WMFT	15 tasks perf. time (seconds)	579.79	567.8	485.09	229.04
	FAS	37	40	44	49

left," and we set this as the treatment goal. Based on this, we adopted the hospital treatment plan of providing OT focusing on reducing contracture and spasticity of the finger joints and increasing sensory function of the hand finger, while delivering low-frequency rTMS to the hand finger area of the primary motor cortex in the unaffected hemisphere on a daily basis.

Content of Rehabilitation Program (at Admission for the Second Time)

(i) Low-frequency (1 Hz) rTMS to the hand finger area of the primary motor cortex in the right (nonlesional) hemisphere (40 minutes once daily)
(ii) Stretching aimed at reducing the muscle tone of the elbow joint and finger joints and reducing contracture of the right ring finger (focusing on any increased muscle tone observed during self- training)
(iii) Facilitation of right wrist dorsiflexion and right finger joint extension for holding reins
(iv) Mobilization and facilitation training of the trunk, neck, and scapular muscles for adjustment of the alignment of the trunk and scapula (including improvement of the subluxation)
(v) Facilitation of flexion of right finger joints and sensory re-education training for surface and deep sensation for gripping and holding reins
(vi) Similar movement training for gripping and manipulation of reins
(vii) Muscle output force adjustment tasks and sensory re-education training for motor ataxia
(viii) Low-frequency therapy on right wrist dorsiflexors (30 minutes daily)
(ix) Self-training focusing on stretching and reflex facilitation training for flexibility and adjustment of alignment of trunk and pinch movement training for extension and flexion of the right finger joints

Course

Regarding the patient's rein movements, motor ataxia was evident during reaching movements, and smooth opening and closing of the hand finger and total gripping of the reins were impossible because there was joint contracture in the ring finger. During rein manipulation, the trunk and scapula were unstable, the neck and trunk were being extended, and there was a risk of falling backward. We, therefore, provided rehabilitation aimed at (i) reducing joint contracture and motor ataxia and smoothly holding the reins, (ii) improving gripping and holding of the reins by improving sensory and grip function, and (iii) improving stability of the trunk and scapula.

As a result, on Day 8, contracture of the ring finger was reduced and ROM improved, and the patient was able to hold reins smoothly. At this time, the patient herself also said that it was easier to open her fingers. On Day 10, improvement of the rein gripping sensation in the hand finger area was confirmed. At discharge, stability of the trunk and scapula during rein manipulation had improved, and manipulation with the upper limb peripheral part was possible. Also, knot tying with both hands, the movement of sitting up from the paralyzed side, and gripping a plastic bottle with the right hand were also possible, and, as shown in Table 7.3, marked improvement was observed especially in WMFT. The patient herself also fully understood the need for the rehabilitation program and self-exercise and worked hard throughout.

Discussion

The patient presented with moderate right upper limb hemiparesis and, in everyday life, used the right upper limb as an assistive hand, but there were also many ADL in which she could not use the right upper limb due to abnormal alignment of the trunk and scapula, right ring finger contraction, and sensory impairment. When we carried out NEURO-15 the first time to treat such conditions, improvement such as the attainment of eating movements with a chopstick-type self-help device and nail-cutting movements in addition to improvement of the upper limb motor function were possible. Following NEURO-15 for the second time, gripping a plastic bottle with the right hand, knot-tying with both hands, and rein gripping movements, which were the target movements, became possible due to further improvement in upper limb motor function and sensory function. We believe that, in this patient, NEURO-15 for the first time resulted in improvement in the disuse of physical functions and triggered a change in behavior, i.e., "using the paretic upper limb in daily life," while NEURO-15 for the second time brought about improvement in physical functions in a true sense, and the quality and frequency of use of the paretic upper limb and the extent of use increased.

The change in the cerebral cortical activity as a result of NEURO-15 lasts for several months after treatment and appears to be extended further through the continuation of rehabilitation. We believe that because we continued rehabilitation on a regular basis following discharge for the first time, the change in the cortical activity was maintained. We also believe that NEURO-15 for the second time resulted in increased effectiveness, bringing about further improvement in motor function. However, we believe that the effectiveness of NEURO-15 could not be fully demonstrated due to the presence of organic changes such as muscle atrophy, joint contracture, and joint deformity. It is, therefore, important to continue regular exercise (rehabilitation) to prevent and improve restriction of ROM and muscle atrophy. In the future, we intend to explain the need for regular self-exercise and rehabilitation after discharge as part of our discharge guidance. This patient has a history of depression, but there was no sign of any recurrence as a result of rTMS treatment.

It was judged, therefore, that it is safe to deliver rTMS treatment provided there are no symptoms of depression at the start of therapy.

Patient Impressions

> I am now able to extend my fingers and hand fairly well and so I have started using them a bit more in everyday life. I think I am also now able to grip reins. When I go home, I want to try it out. I am now able to wash my hands with both hands and can also tie knots. I would like to receive treatment again next year.

Conclusion

We treated this patient, who had already undergone NEURO-15, with NEURO-15 again, taking into consideration joint contracture of the ring finger, motor ataxia, and sensory impairment. As a result, hand finger opening and upper limb motor function showed improvement both subjectively and objectively compared with the first time, and the target movements also became possible. This suggests that carrying out NEURO-15 multiple times may be a useful therapeutic intervention for firmly establishing the change in the cerebral cortical activity and increasing improvement of motor function.

Case 4

A 56-year-old male patient for whom NEURO-15 not only improved motor function but also increased life motivation.

Medical History and Background

In September 2011 (at the age of 55), the right-handed patient developed cerebral infarction (due to right middle cerebral artery occlusion), with speech difficulties and weakness of the left side of the body when he got up. After being given preservative acute phase treatment at the neurosurgery department of a nearby general hospital, he was hospitalized in a convalescent rehabilitation hospital for approximately 2 months and given rehabilitation for left hemiparesis. However, since noticeable paresis of the left upper limb and hand finger remained, in February

2012, he was hospitalized in our hospital for intensive rehabilitation. The patient had no medical history. He used to belong to a soccer club and became an instructor while continuing to play actively and taught children soccer. He later assumed an administrative position and did desk work, but, after onset, he resigned from his post as elementary school principal and took leave. However, he planned to return to work the month after discharge from this hospital, and his reassignment to the education affairs department had been decided. He strongly wished for recovery and also showed signs of a loss of life motivation. He lives with his wife.

Pretreatment Physical Findings

[General physical findings] Height 181 cm, weight 73 kg.
[Consciousness] Clear
[Higher brain function] Mild generalized attention disorder and executive dysfunction are evident. Trail Making Test (TMT)-A score was 77 seconds, and TMT-B was stopped due to signs of altering attention during the test. During evaluation, his expression was stern, with downcast eyes, and he seemed slightly in a daze.
[Motor system] Marked hemiparesis accompanied by increased muscle tone is evident in the left upper limb and left hand finger. Upper limb BRS is equal to stage V, but compensatory movements are noticeable, and difficulties with coordinated movements were seen. Hand finger BRS is equal to stage IV, full extension is difficult, and adduction of the thumb during pinching movements was observed.
[Sensory system] No obvious decline
[Standing and walking] The patient is fully capable of walking independently both indoors and outdoors. There was no particular sign of increased muscle tone, and lower limb BRS was equal to stage V. However, the left lower limb provides less support, left ankle dorsiflexion is insufficient, and reduced clearance is observed.
[ADL] A reduction in shoulder girdle support and stability was observed, compensatory movements were noticeable, and, since putting arms through sleeves in confined spaces was difficult, assistance with upper-body dressing movements and bathing was required. However, the patient performed other movements independently.

Evaluation Results

The results of each evaluation performed between the time of admission and 6 months after discharge were as shown in Table 7.4.

Table 7.4 Evaluation results (Case 4)

Evaluation method/items		At admission	At discharge	4 wks after discharge	4 weeks after discharge
BRS	Left upper limb	V	V	V	V
	Left hand finger	IV	V	V	V
Ueda's 12-grade motor function test for hemiplegia	Left upper limb	10	11	10	10
	Left hand finger	7	10	10	10
MAS	Wrist flexor muscles	1	1	1	1
	Finger flexor muscles	1	1	1	8
FMA (upper limb)	Overall score	48	57	54	54
WMFT	15 tasks perf. time (seconds)	655.08	74.42	294.16	188.07
10 second test (times)	Grip and release	0	7	8	8
Grip strength (kg)		8.8	10.5	11.6	7

Pretreatment Image Findings

A low-density area in the right putamen to corona radiata was observed on the head plain CT.

Patient's Needs, Treatment Goal, and Treatment Plan

The patient strongly wished for recovery of upper limb hemiparesis, but his needs in real life were unclear and vague. Therefore, upon consultation with the patient himself, we set the treatment goal of "independence in upper-body dressing movements," for which he required assistance, and "putting gloves on smoothly," which required time when going out. Based on this, we adopted the hospital treatment plan of providing OT focusing on stretching and facilitation, while delivering low-frequency rTMS every day for 15 days.

Content of Rehabilitation Program

(i) Low-frequency (1 Hz) rTMS to the hand finger area of the primary motor cortex in the left (nonlesional) hemisphere (20 minutes twice daily)
(ii) Stretching aimed at increasing the extensibility and flexibility of the shoulder joint, elbow joint, wrist, and finger joint flexor muscles with special focus on

the pectoralis major muscle, biceps brachii, flexor carpi radialis muscle, flexor carpi ulnaris muscle, flexor digitorum superficialis muscle, and flexor digitorum profundus muscle

(iii) Facilitation of upper limb and placing in recumbent position aimed at increasing stability of shoulder joint and elbow joint

(iv) Space holding movement training of upper limb: incorporating stretching as required, aimed at increasing shoulder girdle support and left upper limb endurance

(v) Wrist dorsiflexion movement training: with the addition of low-frequency therapy for 15 minutes each time, performed aiming at increasing the strength of the dorsiflexors. Having the patient perform dorsiflexion movements voluntary to coincide with the low-frequency contraction rhythm

(vi) Pronation/supination movement training: ring exercise, incorporating visual feedback

(vii) Pinch movements and object gripping training: peg, marble, and coin pinching movement training

(viii) Guidance on self-exercise, focusing on stretching upper limb proximal muscles and distal muscles, dexterity and isolated movements

Course

Motivation for rehabilitation of the upper limb and hand finger was high, and, from the day following admission, we provided rehabilitation to improve shoulder girdle support, stability, and endurance and rehabilitation focusing on the wrist and dexterity training including dorsiflexion movements and object gripping. As a result, from approximately Day 4 in hospital, slight hand finger extension with wrist dorsiflexion began to be observed, and the patient himself also started saying things like "It feels like it will move" and "my shoulder is lighter." At discharge, comments such as "I am now able to put my jacket on by myself," "I am now able to open my hand and grasp things," "It is easier to put gloves on," and "I can now put my socks on with both hands" were evident, and we were able to achieve the treatment goal. As shown in Table 7.4, marked improvement especially for the FMA hand finger item was observed. The patient himself also fully understood the need to carry out the rehabilitation program and self-exercise and worked hard throughout.

Discussion

This patient underwent rehabilitation focusing on PT and OT at a nearby hospital for 4 months after onset, but, since marked paresis of the left upper limb and right hand finger remained, he wanted proactive treatment for this, and this led to treatment with rTMS at our hospital.

The needs of this patient were “to get dressed independently” and “to put gloves on smoothly.” Lower body dressing movements were independent, but upper body dressing required assistance, as forced movements accompanied by compensation were obvious due to a reduction in shoulder girdle support, stability, and endurance. For this patient, whose reinstatement to the education affairs department from the month following discharge had been decided, independence in ADL was considered essential.

In view of this, we provided rehabilitation for attainment of the target movements. We were able to reduce compensatory movements and strengthen the proximal part by carrying out training to increase the support of the shoulder girdle portion, and upper-body dressing movements became possible and the patient became independent. Regarding the hand finger, since marked adduction of the thumb was evident during pinching movements, we corrected this to abduction of the thumb by incorporating visual feedback and positive feedback leading to self-exercise and doing exercises such as marble and coin pinching. Moreover, the patient was very motivated about the rehabilitation and demonstrated an attitude of actively working on each training task and self-exercise. It was observed that this kind of positivity also led to improvement in hand finger movements.

Patient Impressions

> Initially, I was concerned about the nature of rTMS treatment, but when the therapy started, these concerns also disappeared. Ultimately I could be treated without pain or discomfort.
>
> As the days go by, the function of my hand improves and I realize that I now feel I can use my hand in daily life. I learned that the good cycle where I use by my hand because I feel I can and its function improves because I use it is important. I am once again determined to ‘get back a left hand that works’ so I get back to my old self. I will work hard at rehabilitation to achieve this.

Conclusion

This patient strongly wished for recovery from upper limb hemiparesis but demonstrated a decrease in life motivation. On this occasion, the patient experienced a functional recovery which led to an improvement in ADL, and life motivation improved further as a result of carrying out NEURO-15. Functional improvement also led to the confidence to return to work.

Case 5

A 57-year-old male patient with right upper limb hemiparesis accompanied by limb ataxia whose handwriting ability improved as a result of NEURO-15.

Medical History and Background

In August 2009 (at the age of 55), the left-handed patient developed intracerebral hemorrhage (left thalamus), and right hemiparesis accompanied by ataxia, and aphasia occurred. After receiving conservative treatment at a nearby acute phase hospital, he was admitted to a convalescent rehabilitation ward. He underwent rehabilitation in hospital for approximately 3 months, and, once he became independent in walking and ADL, he was discharged and allowed to return home. He later received rehabilitation at this hospital on an outpatient basis approximately once monthly but was hospitalized in our hospital for the purpose of NEURO-15 aimed at further improving upper limb motor function. The patient had a history of hypertension and hyperlipidemia and was taking medication including antihypertensive and lipid-lowering agents. He lived with his wife, worked in company management, and remained in management after onset. His job required a high degree of dexterity with both hands, but he was doing his job to the extent he could using his hand on the nonparalyzed side.

Pretreatment Physical Findings

[General physical findings] Height 165 cm. Weight 62 kg. He was left-handed but had been eating and writing with his right hand before onset.

[Consciousness] Clear

[Higher brain function] No abnormality. MMSE score was 30/30.

[Cranial nervous system] No abnormality

[Motor system] Right hemiparesis (BRS equal to stage VI for upper limb, stage VI for hand finger) and thalamic motor ataxia were observed. Isolated movements of both the upper limb and hand were possible but were slow and clumsy. Support of the upper limb proximal portion was low, and there was a tendency for increased shoulder joint adduction and tension of the adductor muscles. High tension of the pectoralis major muscle, biceps bracchi, trapezius muscle, and latissimus dorsi muscle was observed. Reaching movements were forced and were movements accompanied by extension of the trunk to increase stability, and spatial control of the upper limb was difficult. When pinching small objects such as pins or beans, the muscle tone of the thumb and index finger increased, and coordinated pinching with the finger pads was insufficient. In the finger-to-nose test, moderate tremor was observed, and motor ataxia tended to increase as a result of fatigue.

In movements of both hands in ADL such as washing face, tying tie, and putting on socks, the patient sometimes used the paretic hand as an assistive hand. However, manipulation of tools with the paretic hand was difficult, and the patient had no experience of using chopsticks with the paretic hand. Gripping a pencil with the paretic hand was possible, but handwriting was performed in a forced posture,

involving lateral bending of the trunk to the nonparalyzed side. Distortion was evident in both straight and curved lines, and writing characters of the same size was also difficult (Fig. 7.1). MAS was 0 for shoulder, elbow, wrist, and finger joint flexor muscles. Deep tendon reflexes were (−) for upper limb and (−) for lower limb.

[Sensory system] Surface sensation was moderately dull in both the upper limb and hand finger. There was no clear decline in deep sensation, and the patient did not complain of numbness.

[Standing and walking] The patient was walking stably and independently both indoors and outdoors.

[ADL] The patient performed ADL, including taking a bath, independently. He took meals using chopsticks with the nonparetic upper limb and resting the paretic upper limb on the table. He could go out alone without any problem.

Evaluation Results

The results of each evaluation performed at admission and at discharge were as shown in Table 7.5.

Pretreatment Image Findings

A low-density area suggestive of old infarction lesion from the left thalamus/posterior limb of internal capsule to the left corona radiate is evident in head CT. Low-density areas were also observed in the white matter of bilateral frontal lobes, brain stem, and cerebellar vermis.

Table 7.5 Evaluation results (Case 5)

Evaluation method/items		At admission	At discharge
BRS	Right upper limb	VI	VI
	Right hand finger	VI	VI
FMA (upper limb)	Overall score	60	61
	Item A	34	34
	Item B	10	10
	Item C	14	14
	Item D	2	3
WMFT	15 tasks perf. time (seconds)	39.2	35.9
STEF		32	48
ICARS[a]		19	17

[a]ICARS (international cooperative ataxia rating scale)

Patient's Needs, Treatment Goal, and Treatment Plan

The patient's needs included "wanting to use right hand without tremor, wanting to eat something with chopsticks using right hand and wanting to write some letters with right hand." We, therefore, set "being able to eat all three daily meals using a chopstick-style self-help device in the right hand and being able to write more neatly" as treatment goals for him. Based on this, we adopted the hospital treatment plan of providing rehabilitation focusing on improving trunk and upper limb proximal portion support and improving upper limb and hand finger function, while delivering low-frequency rTMS to the nonlesional hemisphere on a daily basis.

Content of Rehabilitation Program

(i) Application of low-frequency rTMS (1 Hz) to the hand finger area of the primary motor cortex in the right (nonlesional) hemisphere (20 minutes twice daily every day).
(ii) Training to improve support of trunk and muscles surrounding the shoulder girdle: induction of movement of shoulder girdle accompanied by muscle activity of the abdomen aimed at improving isolated movements of the spine and shoulder girdle. Wrapping band around trunk to stabilize trunk and area surrounding shoulder girdle from the outside and to increase the activity of the upper limb.
(iii) Training to improve support of upper limb proximal portion: Gradual progression from holding therapy ball or rod on desk to holding upper limb in space, aiming for contraction of deltoid muscle, triceps brachii, and supraspinatus muscle. When shoulder joint adduction and tension of the adductor muscles tended to increase, we encouraged active movement, inducing movement manually. We also provided theraband exercises for the purpose of increasing activity of the rotator muscles.
(iv) Upper limb function training: repetitive training using objects, focusing on hand posture and reach, grasp, release. Intensive training of gross motor movement, gradually inducing trunk rotation and gradually changing the direction to sideward and backward and the distance.
(v) Dexterity training: handwriting training and repetitive training focusing on object manipulation tasks aimed at regaining coordinated muscle force output control of upper limb and hand finger. We used objects of varying sizes and materials including theraplast, building blocks, beanbags, and counters; gave feedback on the weightiness of the object; and sought adjustment of muscle force output.
(vi) Self-exercise guidance: provided immediately after intensive OT (60 minutes twice daily). Consisted in training to improve proximal portion support according to training described above followed by dexterity training.

We increased experience of perceptual exploratory activities from peripheral portion by focusing on activity of rolling and unrolling newspaper, handwriting training, and dexterity training using paretic hand. Practice using chopstick-style self-help device was implemented at actual mealtimes.

Course

From the day following admission, we provided rehabilitation focusing on training to improve support of the trunk and upper limb proximal portion and dexterity training. On Day 6, the patient began making comments like "I was not able to sense the weight and feel of objects before, but sensation around my thumb is clearer and my hand is now more stable." The patient also fully understood the need for the rehabilitation program and self-exercise and worked hard throughout. At discharge, the patient was able to eat all three daily meals using a chopstick-style self-help device in his paretic hand, and also in his handwriting, both straight lines and curved lines were less distorted (Fig. 7.14). The patient himself said that "My hand is easier to use now than when I was admitted," and he was motivated to train by himself after his discharge. As shown in Table 7.5, ICARS improved from a score of 19 to 17, and STER improved from a score of 32 to 48.

Discussion

Motor ataxia due to thalamic lesion is called thalamic ataxia and is characterized by the occurrence of motor ataxia on the opposite side of the thalamic lesion. Thalamic ataxia has reportedly been found in approximately 25 % of stroke patients with thalamic lesion, but these are often considered divided into three types: those accompanied by motor paralysis (ataxic hemiparesis), by sensory disturbance, and by both. In most patients presenting thalamic ataxia, disturbance of the ventrolateral thalamic nucleus is observed, and it is understood that thalamic ataxia occurs because the dentatorubrothalamic tract, which is formed by efferent fibers from the cerebellum, is damaged.

Since this patient presented ataxia accompanied by motor paralysis and sensory disturbance (hypesthetic ataxichemiparesis) due to thalamic lesion, he could not use the paretic upper limb and hand finger as a functional hand, though capable of isolated movements to some degree. He also had no choice but to go about his daily life without using his paretic hand, to prevent his trembling hand from being seen at work or when eating out.

When manipulating objects, this patient increased movements to compensate for reduced upper limb support, and coordination of agonist and antagonist muscles was difficult. He was, therefore, unlikely to be able to perceptually explore information from the peripheral portion, rendering proper regulation of muscle output force

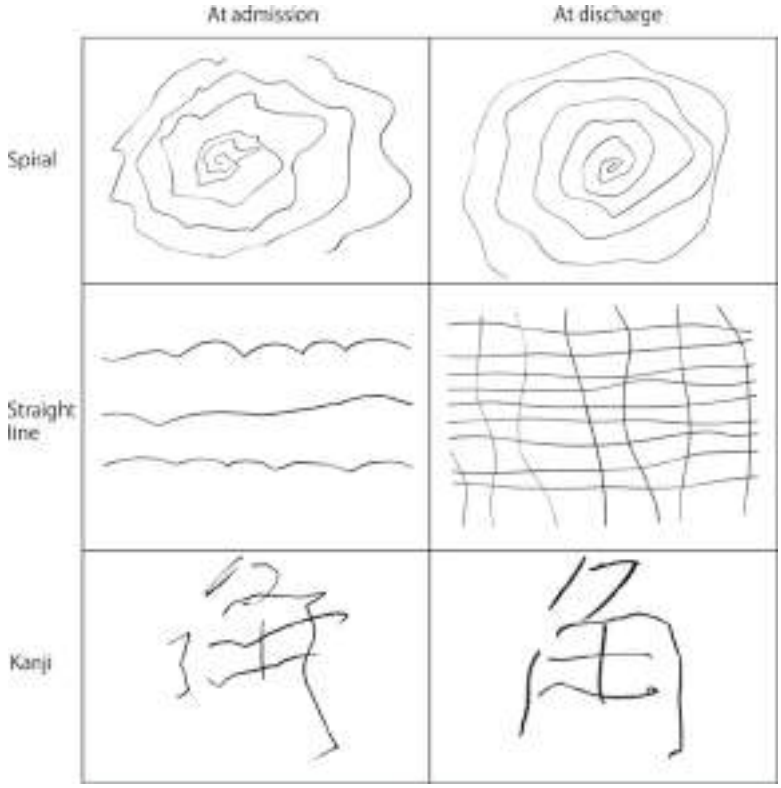

Fig. 7.14 Comparison of handwriting at admission and at discharge

and direction of movement and upper limb control difficult. We, therefore, thought that it was necessary to improve the support of the proximal portion of the upper limb and gradually increase selective use experience of the hand.

More specifically, we wrapped a band around the trunk to stabilize the unstable muscles surrounding the shoulder girdle from outside and then undertook object manipulation. We also incorporated a great deal of theraband exercise and object manipulation performed while checking the resistance and weightiness of the objects. Through these trainings, we expected to draw out selective and smoother movements of the hand based on the provision of feedback both visually and tactually. As a result, flexibility of the muscles and support of the upper limb were obtained, and coordinated movement of the upper limb and hand finger was better than before. We believe that in fact isolated movements were possible and we were, therefore, able to start object manipulation training using many tools, and muscle training from an early stage also has a positive impact on improvement of upper limb function.

It is noteworthy that, as a result of improvement of hypertonia in the forearm and hand finger during exercise, this patient commented that “sensation around the

thumb was clearer" and "it was easier to use my hand." This is presumably because plastic changes accompanying the release from interhemispheric inhibition induced by rTMS facilitated coordinated movement of the upper limb and created a situation more easy than perceptual exploratory activities from the peripheral portion. Based on this, we believe that reduction of compensatory movement and encouragement of selective movements of the hand which are facilitated in intensive OT resulted in increased ability to perceive resistance from objects. This enabled control of muscle force output in the upper limb and hand finger according to the object and appears to have led to improvement in the manipulation efficiency of the hand finger. rTMS appears to be effective for the treatment of thalamic ataxia. However, further research into whether stimulation to the motor center of the hand or the cerebellum is more effective is expected in the future.

Patient Impressions

> I was able to concentrate entirely on my own body for two weeks and I have since been more motivated about self-exercise. I was able to confront this illness with a positive frame of mind. At home, I am eating meals using the chopstick-style self-help device introduced to me by the hospital.

Conclusion

We made use of this patient's comparative ability to perform isolated movements, and, from an early stage, we provided training to improve support of the upper limb proximal portion and dexterity training using objects, in combination with rTMS treatment. As a result, object manipulation speed, pinching movements, and ataxia when using tools improved. This suggested that NEURO-15 can be a useful therapeutic intervention for improving not only upper limb hemiparesis but also ataxia of the limb.

Case 6

A 49-year-old male patient whose phonological processing has improved as a result of rTMS on the right inferior frontal gyrus of frontal lobe.

Medical History and Background

In March 2009 (at the age of 49), the right-handed patient developed cerebral infarction (extensive infarction in the territory of the left middle cerebral artery), and aphasia and right hemiparesis occurred. He was taken to a university medical center

in the Kanto suburbs, and after receiving acute phase medical care at this center, he underwent ST on an inpatient and outpatient basis at a convalescent rehabilitation hospital. In October 2009, he was examined at this hospital for the purpose of rTMS treatment. He then received ST on an outpatient basis roughly once weekly, and, in September 2010 (approximately 1.5 years after onset), he was hospitalized for 10 days of rTMS treatment. After completion of rTMS treatment, we continued to provide the patient with ST on an outpatient basis with the same frequency as before the therapy.

Before onset, the patient was a company employee (on leave during treatment) and lived with his wife and two children. He had no particular medical history.

Pretreatment Physical Findings

Although right hemiparesis was observed, in ADL, the patient walked independently outdoors using an ankle-foot orthosis and T-shaped cane. There was no clear evidence of dysarthria.

Pretreatment Speech and Higher Brain Function Findings

[Consciousness and general mental functions] While changes of facial expression and spontaneity appeared to be slightly poor, we judged that mental functions related to social contact had been more or less maintained. Regarding nonverbal intelligence, no marked decline was observed in tests, with a score of 34 in Raven's Colored Progressive Matrices test.

[Visual recognition] No abnormal findings

[Action] Slight buccofacial apraxia was observed (Only complex movements such as clicking of tongue were impossible).

[Speech] The results of this patient's standard language test of aphasia (SLTA) before rTMS treatment are shown in Fig. 7.15 (black dotted line). Although auditory comprehension was functional at least at a short-sentence level in everyday conversation, the tests showed a marked decline in comprehension of long sentences with complex structure (oral commands in SLTA). This was considered to be largely attributable to decline in linguistic short-term memory capacities (number counting: ± for three-digit numbers) and decline in syntactic comprehension.

There was marked decline in the quantity of speech, and, apart from standard questions and answers such as his name and "that's right" and "I don't know," almost no meaningful linguistic expression was observed. Likewise in tests, although the patient could name a number of familiar nouns (7/20 for "Naming" in the SLTA), explanation tasks at a sentence level ("Explain picture story," etc. in the

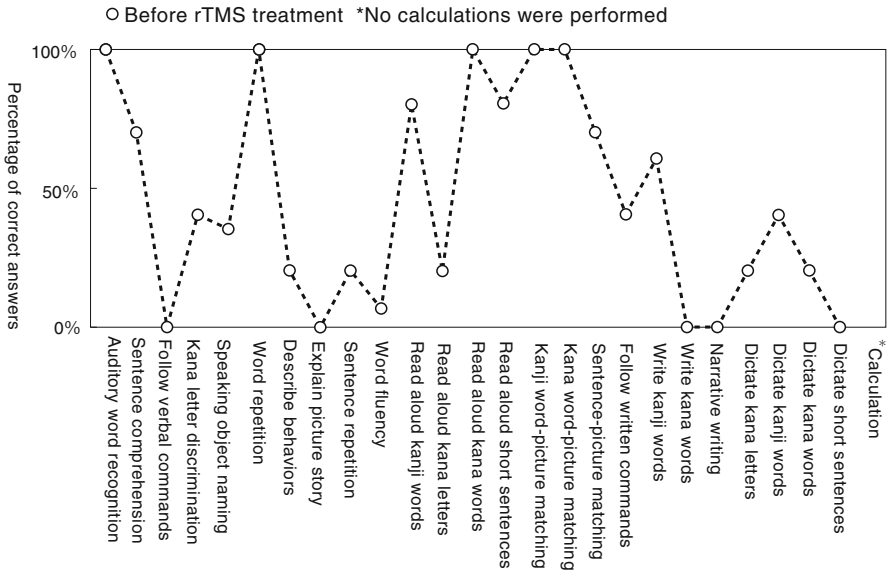

Fig. 7.15 SLTA results (1). Shows the patient's SLTA results before rTMS treatment

SLTA) ended in explanations such as "Like this, like this and then like this (while pointing to the picture)," and the decline in the quantity of information was severe.

As for the causal factors of speech disturbance, problems with multiple processes, including lexical selection, phonological processing, and syntax, were all considered to have a strong impact. In particular, the fact that situations in which the patient answered information about the mora (beats) of the target words, such as "three" or "quite a lot," even though he was unable to name them were seen frequently and the fact that initial sound hints for familiar nouns and verbs were extremely effective suggested clear difficulty in phonological recollection.

On the other hand, given that, in speech, almost no distortion of speech sounds could be heard and that there were almost no speech delays in sequential expressions such as standard questions and answers like those described above and counting from 1 to 10, we judged that anarthria is either not present or slight.

According to the tests, overall, comprehension of written language tended to be better than auditory comprehension. However, especially with regard to kana, although actual comprehension of easy words like those used in the SLTA was possible, reading aloud took time, and the patient demonstrated extreme difficulty reading aloud single kana letters and nonwords. Matching of vocal sounds and kana was also not easy.

Regarding writing, some simple single kanji words could be spontaneously written, and some could be dictated, but spontaneous writing of single kanji words was very difficult, and, also in dictation of vocal sound sequence presented by a tester, the patient was only able to write a very small part such as "HO-N," and there was a severe degree of disturbance.

Overall, the patient was considered to have aphasia characterized by moderate to severe disturbance of phonological fluency and disturbance linking vocal sounds and kana, severe syntactic disturbance (both in comprehension and expression), and moderate disturbance of lexical selection, and the total degree of aphasia was judged moderate to severe. While symptoms rendered clear classification difficult, broadly speaking, we perceived the patient's condition as falling between typical Broca's aphasia without elements of anarthria.

Pretreatment Image Findings

In head MRI images (TI-weighted images), an extensive low-intensity area from the middle frontal gyrus, inferior frontal gyrus, precentral gyrus, postcentral gyrus of left frontal lobe, supramarginal gyrus of parietal lobe, and superior temporal gyrus of temporal lobe to the deep white matter and lateral part of basal ganglia was observed, and, in functional MRI (fMRI) during language tasks, activation in the middle frontal gyrus and inferior frontal gyrus of left frontal lobe was confirmed (Fig. 7.16).

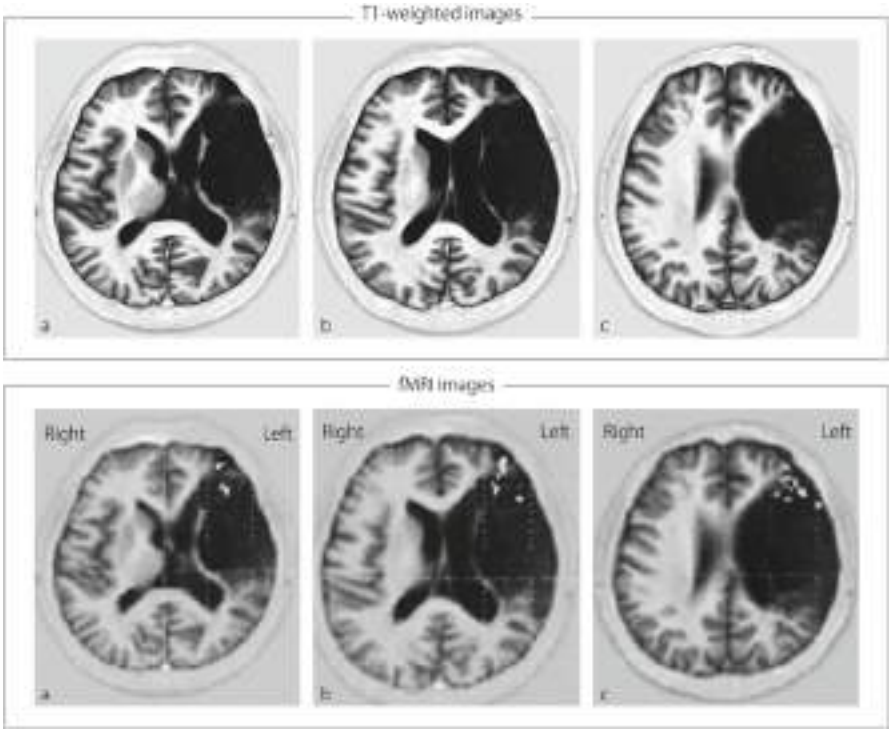

Fig. 7.16 Pretreatment image findings (Case 6)

Patient's Needs, Treatment Goal, and Treatment Plan

The need of this patient was to improve everyday communication skills as much as possible ahead of the fast-approaching time limit for his return to work. However, as things stood, expression at a single-word level was difficult, as stated in pretreatment speech findings.

In view of this, we set a long-term ST objective (in several years' time, including rTMS treatment) of "communicating short sentences that include a noun and a verb and have a concrete meaning" and a short-term objective (in several months' time) of "communicating information by expressing nouns or verbs that have concrete meaning at a single word level."

We adopted the treatment plan of "first aiming, as a top priority, for improvement in phonological recollection, which though severely disturbed is considered essential for expression at a single word level, and carrying out training with respect to the lexical selection process and syntax, as an extension of this."

Content of Rehabilitation Program

(i) Application of low-frequency (1 Hz) rTMS to the right inferior frontal gyrus (40 minutes per session for 10 days).

(ii) Provision of one-to-one ST for approximately 60–80 minutes each day (content during hospitalization for rTMS and during outpatient training before and after hospitalization is almost the same). Intervention focusing on phonological recollection and vocal sound and kana processing tasks in a broad sense in accordance with the aforementioned plan. Specific tasks included (1) vocal sound position in word identification and extraction tasks, (2) reversal of words with two to three moras that do not include special syllables, (3) construction of kana single words through selection from a group of kana characters containing dummies in response to pictures, (4) mora number recollection and naming with sound from end of or interior of word as a hint in response to pictures, and (5) reading aloud short sentences.

(iii) Distribution of printouts for self-exercise, with same content as for one-to-one ST (especially task of constructing kana single words through selection and copying from a group of characters).

Short-Term Evaluation Results

Table 7.6 shows this patient's speech function evaluation results directly before and after rTMS treatment. Before therapy is before the start of treatment on the first day after admission, and after therapy is the evaluation on the final day, directly after

Table 7.6 Evaluation results (Case 6)

Evaluation method/items			Before therapy	After therapy
SLTA-ST (assistive test)	Naming (no. of correct answers out of 40 words)[a]		12	10
	Explain picture story (Graded assessment: 6 is highest out of 6 grades)	1. Angler	2	2
		2. Chestnut tree	2	2
		3. Black cat and white cat	1	1
		4. Bird and whale	1	2
WAB	Repetition (score out of a total of 100)		40	44

[a]"Naming" in SLTA-ST is performed before and after treatment by splitting 80 words into two groups (40 words each) with no difference in the percentage of correct answers, with reference to the percentage of correct answers of 253 patients with aphasia and others at the time of test preparation shown in the manual

completion of the entire treatment schedule. In "Explain picture story" of the supplementary tests for standard language test of aphasia (SLTA-ST), although improvement in the graded evaluation was evident for one item only, overall, there was no substantial change.

Long-Term Evaluation Results

Figure 7.17 shows this patient's SLTA profile before and after rTMS treatment and approximately 1 year later. In this case, before therapy is directly before admission, and after therapy is 3 months after discharge. In the evaluation after therapy, the items that show clear improvement were the three items "Speaking Object naming," "Read aloud kana letters," and "Write kana words."

Course

As shown by the evaluation results, there was no significant change in symptoms during rTMS treatment in hospital or immediately after treatment, and the patient himself also sometimes stated (in the form of a Yes-No question) that "since my stroke onset, I feel that, whatever I do, my symptoms are, if anything, getting rapidly worse."

However, from approximately 2 to 3 months after therapy, the naming of high-frequency nouns, which was used in tasks, became easier, and the patient was increasingly able to name things immediately even without recalling the number of moras and hints. At the same time, situations in which the reading aloud and writing of kana, which was difficult before, gradually became possible began to be seen

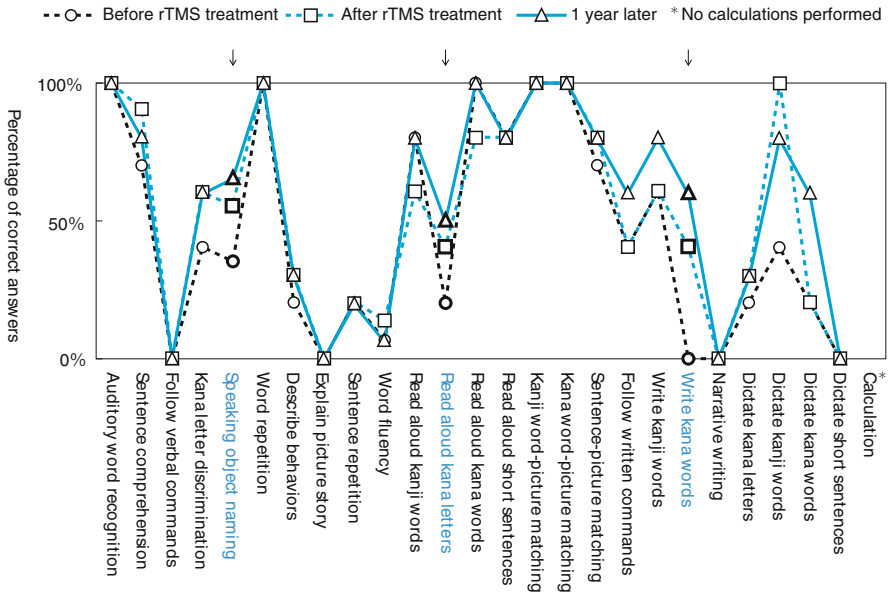

Fig. 7.17 SLTA results (2). Shows the patient's SLTA profile before and after rTMS treatment and approximately 1 year later

frequently. In the SLTA 3 months after therapy (Fig. 7.17) (blue dotted line), a clear change was observed, with the outcome for "Naming" improving from 7/20 words to 11/20 words and the patient smoothly writing 2 words in "Kana single word writing," which had been completely impossible before. Moreover, in "Naming," whereas the 7 words correctly answered before therapy were all grade 5 according to the scoring standard (correct answer from 4 seconds), in the SLTA after therapy, 10 out of the 11 correctly answered words were grade 6 (correct answer within 3 seconds), indicating a marked change in quality. However, on the other hand, difficulty naming low-frequency words remained the same as at the time of the test before therapy.

Later, also in everyday conversation, expression of meaningful single words was facilitated, and also in outpatient ST, the patient became able to progress to training in new areas such as tasks relating to the semantic lexical selection process and tasks relating to syntax. Figure 7.17 also shows SLTA scores after 1 year (blue solid line), and "Naming" and kana-related items which showed clear improvement after 3 months had almost all improved further after 1 year.

In terms of life, thanks to his company's generous support system, the patient gradually achieved a return to work from approximately 4 months after rTMS treatment. Initially, his duties consisted of non-language-type duties (e.g., delivering postal items to each department within the company) but later expanded to include duties such as numerical input into spreadsheet software using a computer.

Discussion

While there is a great deal of literature reporting improvement in naming as an effect of rTMS treatment in patients with aphasia, there is almost no literature that goes as far as mentioning the processes in which this improvement takes place in light of the cognitive-neuropsychological models for naming which we, as clinicians including speech therapists, use on a daily basis.

In this patient, the pattern of this improvement in naming was characterized not by the fact that the score for naming low-frequency words, whereby the word itself is difficult to identify, improved but by the fact that the patient became able to quickly and reliably name high-frequency words. Given that reading aloud and writing of kana improved at the same time, the marked improvement in language function gained during the 3 months or so after rTMS treatment can be considered to relate mostly to phonological recollection.

For this patient, since disturbance of phonological recollection and the need to improve this were already clear right from the outset, at the time of the initial evaluation, we provided training focusing on this prior to the initiation of rTMS treatment. As an underlying mechanism of improvement in this case, it is considered that the combined use of rTMS treatment and ST synergistically improved the outcome, as the target site of the rTMS determined based on the results of the fMRI and the effect of rTMS were perfectly consistent with the speech training plan.

Conclusion

For this patient, improvement in disturbance of phonological recollection and the related processes of naming and kana reading aloud and writing was observed over a comparatively long period as a result of the combined use of rTMS on the right inferior frontal gyrus of frontal lobe and ST. For this patient, we felt that rTMS treatment may have acted as a catalyst for long-span ST in the chronic phase.

Case 7

A 78-year-old male patient for whom bilateral rTMS and intensive swallowing rehabilitation were undertaken as a treatment for dysphagia after medullary infarction.

Medical History and Background

In April 2011 (at the age of 77), the right-handed patient presented with trunkal ataxia and dysphagia. He was diagnosed with medullary infarction and urgently admitted to a nearby general hospital. After undergoing conservative treatment, he was able to walk independently, but the dysphagia remained and he was, therefore, discharged home from hospital in a fasting state, having undergone gastrostomy. Although he subsequently underwent outpatient dysphagia rehabilitation at the same hospital, no improvement of swallowing functions was observed. Consequently, in March 2012, he visited our hospital's outpatient department and began to receive outpatient dysphagia rehabilitation once weekly, including stretching with a balloon. However, endoscopic evaluation of swallowing showed failure of initiation of the swallowing reflex and saliva aspiration, and oral intake remained difficult. Therefore, in June 2012, the patient was hospitalized for 7 days for the purpose of rTMS treatment for dysphagia. The patient had no particular medical history. He was taking antiplatelet agents. He lived with his wife.

Pretreatment Physical Findings

[Consciousness] Clear. No major abnormality with higher brain function.
[Swallowing function] Choking and wet hoarseness are observed as a result of the intake of thickened water.
[Motor system] There is no clear motor paralysis of the four limbs. The patient is stable standing and walking.
[Sensory system] There is thermal hypoalgesia of the right side of the face and left upper and lower limb.
[ADL] Independent

Evaluation Results

The results of each evaluation performed at admission and at discharge were as shown in Table 7.7.

Pretreatment Image Findings

A low-density area indicating an old infarction lesion in the right lateral medullary region was observed on a head plain CT. In addition, videofluorgraptic (VF) examination using barium jelly revealed failure of initiation of the swallowing reflex,

Table 7.7 Evaluation results (Case 7)

Evaluation method and evaluation items	At admission	At discharge
MASA[a]	149	161
P-A scale[b]	4	2
LEDT (seconds)[c]	3.22	1.2
SWAL-QOL (over-all)[d]	611	619
RSST[e]	1	2
FOIS[f]	1	2

[a]MASA (Mann assessment of swallowing ability)
[b]P-A scale (penetration-aspiration scale)
[c]LEDT (laryngeal elevation delay time)
[d]SWAL-QOL (the swallowing quality of life)
[e]RSST (repetitive saliva swallowing test)
[f]FOIS (functional oral intake scale)

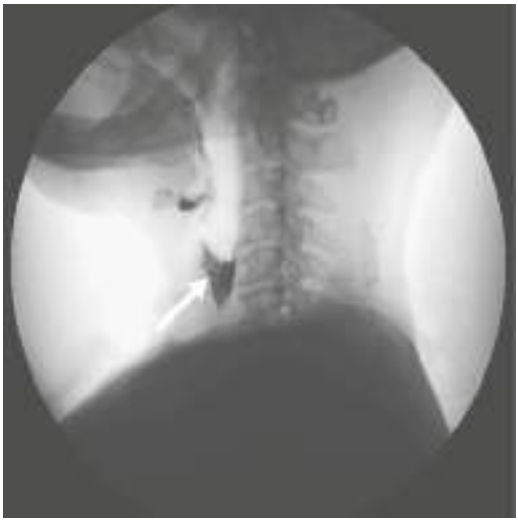

Fig. 7.18 Pretreatment image findings (Case 7) Pharyngeal residues of barium are observed in VF

obstruction of the esophageal orifice, pharyngeal residue, and saliva aspiration after swallowing (Fig. 7.18).

Patient Needs, Treatment Goal, and Treatment Plan

The need of this patient was "to become able to eat all three daily meals by mouth." However, as things stood, dysphagia was severe, and, upon consultation with the patient himself, we, therefore, set the treatment goal as "intake of small amounts of semisolid food." Based on this, we adopted the treatment plan of providing dysphagia rehabilitation focusing on indirect swallowing training in the pharyngeal stage, while delivering rTMS treatment on a daily basis.

Content of Rehabilitation Plan

(i) Application of rTMS (3 Hz) to the pharyngeal area of the bilateral primary motor cortex (10 minutes twice daily).
(ii) Head-raising training: lying in supine position with shoulder on floor and raising head only until toe is visible. "Raising continuously for one minute and then resting for one minute" three times through. If pulse is 120 beats per minute directly after raising, load is adjusted to prevent this.
(iii) Balloon stretching training: "Simple withdrawal technique" which involves swallowing 14 Fr Foley catheter and then inflating and withdrawing balloon is repeated five times per training session.
(iv) Exercising of tongue muscles focusing on dorsum of tongue raising training to increase pharyngeal pressure.
(v) Guidance to complete balloon stretching training for approximately 1 hour and 30 minutes twice daily as self-exercise.

Course

We began rTMS and dysphagia rehabilitation with a speech therapist from the day of admission. As a result, from approximately Day 4 in hospital, the swallowing reflex began to appear slightly easier, and the patient himself also started to say things like "I cough up less saliva." At the time of discharge, the daily amount of tissues necessary to wipe up coughed up phlegm had decreased, and also in the evaluation results shown in Table 7.7, marked improvement especially in the LEDT item was seen, and direct swallowing training using a small amount of jelly was possible. The patient himself also fully understood the need to carry out the rehabilitation program and the self-exercise and worked hard throughout.

Discussion

This patient presented with failure of initiation of the swallowing reflex and obstruction of the esophageal orifice, and aspiration of saliva was also often evident, and he was, therefore, a case in which safe oral intake was difficult. When we delivered rTMS and dysphagia rehabilitation, including balloon stretching, to treat these conditions, unfortunately, on this occasion, our intervention during his time in hospital alone was not enough to lead to the oral intake of all three daily meals. However, since clear improvement in swallowing initiation speed was achieved, this can be considered a step closer to safe oral intake.

While cricopharyngeal myotomy is sometimes considered to treat obstruction of the esophageal orifice as a result of medullary infarction, in cases where initiation

of swallowing is difficult, the oral intake rate after surgery is low, and so surgery is often not indicated. Likewise in this patient, if balloon training proves unsuccessful, indication of surgery for improving function of swallowing will be considered, but then failure of initiation of swallowing will be a problem. Accordingly this time, when proposing the treatment program, we decided to prioritize improvement of failure of initiation of swallowing and subsequently to consider surgery to improve swallowing function.

That said, there is also the possibility that if we apply low-frequency rTMS to the cricopharyngeal muscle, the obstruction will be reduced, and swallowing function will be further recovered. In the future, we believe it is necessary to examine ways of selective rTMS, paying careful attention to individual cases.

Patient Impressions

> As a result of receiving rTMS treatment, the swallowing reflex became easier to occur and the amount of phlegm decreased. In the future, I intend to consider surgery while continuing rehabilitation on an outpatient basis.

Conclusion

When treating this patient, we focused on failure of initiation of the swallowing reflex and provided dysphagia rehabilitation, consisting mainly of training in the pharyngeal phase, in combination with rTMS. As a result, speed of initiation of the swallowing reflex and aspiration of saliva showed improvement both subjectively and objectively. Therefore, combined approach to pharyngeal phase dysphagia rehabilitation and rTMS appeared to be a useful intervention in patients with dysphagia after medullary infarction.

Chapter 8
Future Challenges of rTMS Treatment

1 Combination Treatment of Botulinum Toxin Injection and rTMS Treatment (Naoki Yamada, Wataru Kakuda and Masahiro Abo)

A. What Is Botulinum Toxin Type A?

Clostridium botulinum is the generic name of the bacterium that produces botulinum toxin, and based on differences in the antigenicity of this toxin it is classified into seven types, namely, into type A to G. In 1977, an American ophthalmologist [1] succeeded in treating strabismus by using botulinum toxin type A (BoNT-A) as nonoperative treatment. As a result, BoNT-A began to be used in clinical practice for the treatment of various diseases such as "blepharospasm," "hemifacial spasm," "spasmodic torticollis," and "upper and lower limb spasticity."

From the end of the late 1990s, BoNT-A was widely used in the Western countries for the treatment of upper limb spasticity. In Japan, the use of BoNT-A was finally approved in October 2010 (through the expansion of the indications for its use, which since then also includes upper and lower limb spasticity). For the management of spasticity, it is important to perform BoNT-A therapy combined with rehabilitation. As of December 2012, Botulinum toxin type A products for the treatment of upper and lower limb spasticity that are covered by health insurance in Japan are limited to Botox® which is manufactured by GlaxoSmithKline. Therefore, the use of the signage BoNT-A in this chapter refers only to Botox®.

In vivo Botox® acts on cholinergic peripheral nerves and reduces muscle tonus by inhibiting the release of the neurotransmitter acetylcholine at neuromuscular junctions. Inhibition of the release of acetylcholine causes axonal sprouting in the vicinity of motor nerve endings at which neurotransmission is blocked through this toxin. Sprouting produces collateral axonal branches that repair endplates, thus leading to the formation of new endplates [2]. This nerve regeneration process

M. Abo, W. Kakuda, *Rehabilitation with rTMS*,
DOI 10.1007/978-3-319-20982-1_8

requires 3 to 4 months, which corresponds approximately with the clinical efficacy period of Botox®.

B. Actual Administration of BoNT-A for the Treatment of Upper Limb Spasticity

Upper limb spasticity is typically characterized by flexed postural patterns such as illustrated in the so-called Wernicke-Mann posture (Fig. 8.1) and manifest, e.g., as adduction or internal rotation of the shoulder joint and flexion of the elbow, wrist, and finger joints (the forearm can be pronated or supinated). Obviously, upper limb spasticity affects ADL and reduces QOL [3, 4].

BoNT-A therapy is used for a relatively wide range of indications, and one can try it out if it is expected that "with this therapy upper limb spasticity can be alleviated, and that this will bring relief from pain, or lead to an improvement of some sort of passive or active motions, that also will result in an improvement of ADL and QOL." In patients with severe hemiparesis "facilitating the extension of a passive upper limb joint for reducing the care burden" could also be a treatment goal that is

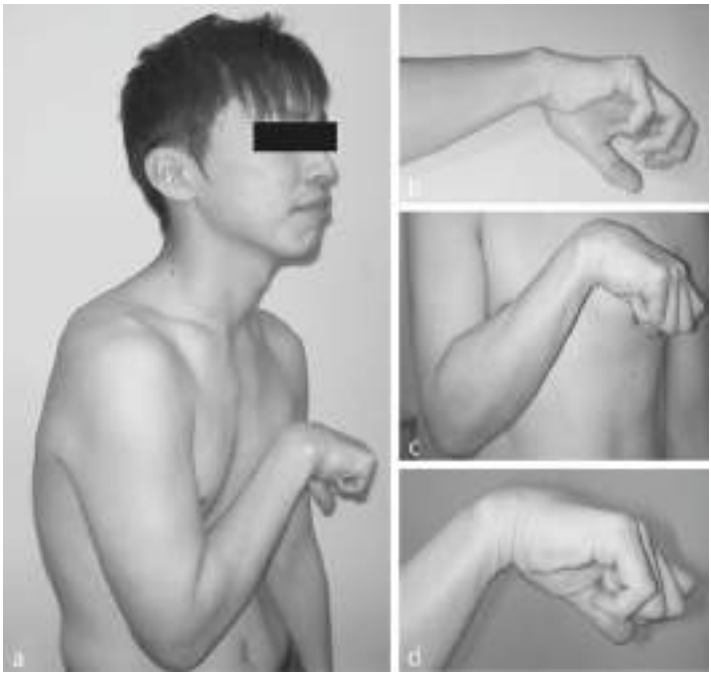

Fig. 8.1 Wernicke-Mann posture
(**a**) Adduction or internal rotation of the shoulder joint, (**b**) forearm pronation, (**c**) elbow flexion, (**d**) wrist flexion

worth to try out this therapy. Pronounced joint contracture and muscle atrophy are no indication for aggressive BoNT-A therapy, but in either case BoNT-A should be administered after having clarified "what treatment goal shall be achieved by its administration."

The muscles into which BoNT-A is injected are "muscles with increased tone that cause these abnormal postures." Therefore, depending on the individual condition of the patient, often four to six muscles are selected for treatment. In particular the following six muscles, namely, the "flexor carpi radialis muscle," "flexor carpi ulnaris muscle," "flexor digitorum profundus muscle," "flexor digitorum superficialis muscle," "flexor pollicis longus muscle," and "adductor pollicis muscle," play an important role in BoNT-A therapy and have also been investigated in studies on BoNT-A therapy that were conducted in Japan. However, in cases with pronounced adduction or internal rotation of the shoulder joint or elbow flexion, BoNT-A is also injected into the "pectoralis major muscle," "latissimus dorsi muscle," and "biceps brachii muscle."

The dose of BoNT-A is determined depending on the degree of spasticity and the volume of muscle into which it is injected. In the case of large muscles such as the pectoralis major muscle or biceps brachii muscle 50–100 units are appropriate, and in the case of other upper limb muscles up to 50 units are considered appropriate. However, at present in Japan, the administration of BoNT-A for the treatment of upper limb spasticity is only covered by health insurance up to a maximum dose of 240 units.

It is not necessary to search for the motor points of the muscles when injecting BoNT-A into muscles of the upper limb. It is likely that a muscle relaxing effect is achieved if the injection needle was inserted into the muscle belly and BoNT-A was unmistakably injected into the muscle. Normally after 2 to 7 days an antispasticity effect is observed, and although there are individual differences, this effect is sustained for approximately 3 to 4 months. It is possible to repeat administration 3 months or more after injecting BoNT-A; however, in this case the original degree of spasticity often returns if the injection of BoNT-A is not used in combination with rehabilitation. In case of upper limb spasticity it is possible to gradually regain the original softness of the muscles by combining treatment with BoNT-A with OT, and we have experienced that lower doses are required for repeated BoNT-A treatment.

As for adverse reactions, it is believed that the possibility of serious complications is very low if upper limb spasticity is being treated by use of BoNT-A, but sometimes an excess muscle relaxing effect is observed (in particular, if, e.g., high doses of BoNT-A were administered compared to the degree of spasticity).

For the main injection sites and methods used when injecting BoNT-A into muscles of the upper limb please refer to Table 8.1. Moreover, based on our experience we have summarized important points and precautions regarding BoNT-A therapy for the treatment of upper limb spasticity in Table 8.2. However, it is not rare that patients think that "after injection of BoNT-A upper limb hemiparesis will improve without fail and that there will be no need to perform rehabilitation," and therefore the goal of BoNT-A therapy and the necessity of concomitant rehabilitation should be sufficiently explained to the patient prior to administration.

Table 8.1 Injection sites and treatment methods used when injecting BoNT-A into major muscles of the upper limb

Name of muscle	Site of injection and method
Pectoralis major muscle	The arm is abducted at the shoulder joint, and the injection needle is inserted while grabbing the muscle together with the subcutaneous fat layer
Biceps brachii muscle	The forearm is supinated, and the injection needle is inserted into the muscle belly in the middle of the upper arm
Brachioradialis muscle	The forearm is pronated, and the injection needle is inserted into the middle point between the biceps brachii tendon and the lateral middle condyle of the humerus
Flexor carpi radialis muscle	The injection needle is inserted approximately 4–5 cm distal to the middle point between the biceps brachii tendon and the medial epicondyle of the humerus
Flexor carpi ulnaris muscle	The injection needle is inserted two fingerbreadths volar to ulnar at a height 1/3 proximal to the forearm
Flexor digitorum superficialis muscle	The forearm is supinated, and the injection needle is inserted through the flexor carpi radialis muscle at the palmar side of the forearm
Flexor digitorum profundus muscle	The elbow is flexed, the forearm is supinated, and the injection needle is inserted 3–4 fingerbreadths distal to the olecranon
Flexor pollicis longus muscle	The injection needle is inserted through the flexor carpi radialis muscle and the flexor digitorum superficialis muscle in the middle of the forearm
Adductor pollicis muscle	The injection needle is inserted into the first interdigit towards the base of first metacarpal bone

Table 8.2 Important points and precautions regarding BoNT-A therapy for the treatment of upper limb spasticity

1.	First the goal of BoNT-A injection (e.g. relief of pain, improvement of passive and active motions) should be clarified. Then this should also be explained to the patient (and the patient's family)
2.	The dose of BoNT-A is determined depending on e.g. the size of the muscle into which it is injected, and the degree of spasticity, however, there are individual differences regarding its efficacy
3.	The patient (and the patient's family) should be fully explained that it is desirable that also after BoNT-A injection rehabilitation (OT) is conducted
4.	The rehabilitation program following BoNT-A injection should be determined depending on the condition of upper limb spasticity of the individual patient
5.	Self-exercise of the upper limb is an important part of rehabilitation following BoNT-A injection
6.	When some sort of rehabilitation intervention for the treatment of upper limb hemiparesis is being performed, and it is judged that the implementation of this rehabilitation intervention is blocked by the spasticity, then BoNT-A should be injected prior to the intervention
7.	Even if the aim is only to improve passive motions, it is possible that in combination with rehabilitation the antispasticity effect of BoNT-A is amplified
8.	If following BoNT-A injection muscle weakness is observed, the patient should be provided sufficient explanation about his/her condition, and be followed up
9.	BoNT-A is an expensive drug, but BoNT-A therapy provides excellent "cost- effectiveness"

C. Use of BoNT-A in Combination with NEURO-15

As outlined in the book by Ward et al. [5], which was published in 2001, that "BoNT-A therapy should be performed in combination with rehabilitation," the concept that BoNT-A therapy should be performed in combination with rehabilitation has been advocated since a long time ago. Also in the International Consensus Statement by Sheehan et al. [6] in 2010 it is stated that "the treatment of upper limb spasticity should be addressed by a comprehensive approach the core of which is BoNT-A therapy," and moreover it is being recommended to combine BoNT-A therapy with rehabilitation.

In April 2008 we started to use low-frequency rTMS in combination with intensive OT at our department. This combination therapy, which we termed "NEURO," was devised by our group and is conducted over a period of 15 days. Since April 2009 we are actively using a 15-day combination treatment protocol termed "NEURO-15" for the treatment of poststroke upper limb hemiparesis. At the present stage, virtually in all patients in whom we tried this therapy, NEURO-15 could be safely completed, and regarding its therapeutic effect, significant improvement has been confirmed for FMA and the performance time of the 15 tasks of the WMFT. However, its therapeutic effect appears to be considerably affected by the degree of spasticity of the upper limb on the paralyzed side prior to treatment, and tends to wane the severer the degree of spasticity of the upper limb.

Therefore, we started a combination treatment in which upper limb spasticity is reduced by performing BoNT-A therapy prior to NEURO-15 [7]. Soon after the use of BoNT-A for the treatment of upper and lower limb spasticity was approved in October 2010, our group actively attempted to perform BoNT-A therapy in patients with spasticity of the upper and lower limb, and from the very beginning we considered it important to adhere to the concept that "BoNT-A therapy should be performed in combination with rehabilitation."

Below, we present "a patient successfully treated with BoNT-A therapy prior to the rehabilitation in order to enhance the efficacy of rehabilitation at the Department of Rehabilitation, Shimizu Hospital, The Kyosaikai Medical Foundation," based on the idea that the presence of spasticity might be an inhibitory factor of rehabilitation. Moreover, we present "motor function evaluation data of patients in whom BoNT-A therapy was performed in combination with NEURO-15" from the same department.

D. Actual Use of BoNT-A Combined with NEURO-15 (Presentation of a Patient in Whom This Treatment Was Remarkably Effective)

1) Medical History, Living Situation

This patient was a 49-year-old woman. In August 2008 she experienced intracerebral hemorrhage and was urgently admitted to a general hospital nearby with right hemiparesis (dominant hand) caused by left putamen hemorrhage. She received

conservative medical treatment and was discharged in October of the same year. Until March 2009 she underwent rehabilitation including OT of the upper limb at the same hospital, but movement disorder of the right upper limb remained. Hereafter, she was provided day service and visiting rehabilitation. However, in September 2011 she was admitted to our department because her condition did not change, and she hoped that "her condition would improve at least a little." She lived together with her husband and two children, and before onset she had been a housewife. At present she mainly uses her left upper limb when carrying out household chores or cooking meals.

2) Physical Findings Before Treatment

Muscle tone of the whole upper limb was increased, and marked in particular during motion. She could neither extend nor relax her fingers, dorsiflexion of the wrist was only possible when extending her elbow, and was not seen when the elbow was flexed. Her wrist was in a contracted state.

Brunnstrom recovery stage (BRS) was stage IV for the upper limb and stage III for hand-finger, but no sensory disturbance was observed. Muscle tension was high in upper limb through the elbow to hand-finger, with MAS of 2–3. Flexion of all fingers and radial abduction of the thumb was slightly possible; however, when grasping objects all fingers were flexed, and the grasped object was clenched inside her hand, because she could not extend her fingers. FMA score for items in the upper limb section was 40 points, and performance time for 15 WMFT tasks was 1090 seconds.

3) The Needs and Treatment Goals of This Patient

The needs of this patient were to be able "to hold a rice bowl while eating," "to hold a cup when drinking liquids," "to eat with chopsticks," and "to write with her paralyzed hand." Therefore, treatment goals were set as follows: to reduce the muscle tone of the whole upper limb, to become able to extend her fingers (in particular the thumb and index finger), to gain pinching motions, to gain grasping movements necessary for holding a cup, and movements that are necessary for using chopsticks.

4) Course of Treatment

In Week 1 a rehabilitation was provided focusing on improving operability and stability of the central upper limb, and reduction of muscle tone of the distal upper limb. Increased muscle tone of the whole upper limb was treated by injecting BoNT-A on Day 3 of hospitalization (biceps brachii muscle: 50 units, flexor carpi radialis muscle: 25 units, flexor digitorum superficialis muscle: 25 units), and by performing mainly physical therapy and stretching exercises. From around the end

of Week 1 a reduction in the muscle tone of the distal upper limb was observed, and she could also voluntarily relax her fingers.

In Week 2 mainly neuromuscular facilitation of the distal upper limb was performed. As for finger extension and dorsiflexion of the wrist, after spasticity of the finger, wrist, and palmar flexor muscle groups had been reduced, finger extension and dorsiflexion of the wrist were encouraged through neuromuscular facilitation. As for the fingers, in particular palmar abduction of the thumb and extension of the index finger were performed, and at the beginning of Week 2 extension of the thumb and index finger, and in the middle of Week 2 pinching motions became possible. At the end of the week the patient was able to eat with a pair of tweezers-shaped chopsticks. The goal to become able to grasp a cup was not achieved because the patient could not sufficiently extend her other fingers, but nevertheless the results of motor function evaluation had improved significantly.

At discharge, MAS was 0–1, FMA score for items in the upper limb section was 50 points, and performance time for 15 WMFT tasks was 558 seconds.

5) Discussion

When we started to treat this patient, 3 years had passed since the onset, and she had no rehabilitation for the previous 1 year. Therefore, a high degree of spasticity and mild contracture of the wrist was observed, and as a result of spasticity it was difficult for her to move the upper limb and fingers of the paralyzed side.

We believe that her motion could be facilitated because reduced spasticity resulted from our treatment focused on spasticity. It has been reported that reduced spasticity is the main factor that leads to the recovery of motor function. As a result of trying to achieve changes in motor function and to reduce spasticity, also in this patient reduced spasticity was observed prior to improvement in motor function. We believe that this treatment approach, in which the reduction effect that BoNT-A therapy and rTMS have on spasticity is combined with rehabilitation specifically designed for the treatment of spasticity, was remarkably effective in reducing spasticity and that this led to the recovery of motor function.

E. Actual Use of BoNT-A Combined with NEURO-15 (Presentation of Data)

A total of 67 poststroke patients who had a stroke more than 1 year before with upper limb hemiparesis (based on the eligibility criteria for NEURO-15) and obvious spasticity received injection of BoNT-A into the paralyzed upper limb (total dose was 100–240 units for, e.g., biceps brachii muscle, flexor carpi radialis and flexor carpi ulnaris muscle, flexor digitorum superficialis and flexor digitorum profundus muscle) within 3 days after initiation of treatment following hospitalization before NEURO-15.

At present in our department NEURO-15 consists of combination treatment with low-frequency rTMS for 40 minutes and intensive OT for 120 minutes over the 15-day hospitalization. We decided to apply in each low-frequency rTMS treatment session at 1-Hz for 40 minutes (total of 2400 pulses) to the hand-finger areas in the primary motor area of the unaffected hemisphere. One treatment session of intensive OT consisted of one-to-one training for 120 minutes and self-exercise for 120 minutes. The one-to-one training, which was conducted with an occupational therapist, was centered on shaping exercises and repetitive motion exercises. Motor function of the upper limb was evaluated by use of, e.g., FMA upper limb evaluation items, performance time for 15 WMFT tasks, and MAS.

As a result, no adverse reactions or adverse events related to BoNT-A injection or the implementation of NEURO-15 were observed in any of the patients. At the time when NEURO-15 was completed significant improvement was observed in FMA scores, performance time for 15 WMFT tasks, as well as MAS (elbow, wrist, and MCP flexor muscle group). The results of motor function evaluation before and after treatment are summarized in Table 8.3.

This shows that BoNT-A injection prior to NEURO-15 improved spasticity, which is an inhibitory factor of rehabilitation, and promoted the effectiveness of NEURO-15 (in particular of intensive OT), and that this eventually led to improved motor function. Therefore we believe that it is desirable that in the future, patients with upper limb hemiparesis who present with spasticity are treated with BoNT-A as a "pre-conditioning procedure" prior to NEURO-15, and rehabilitation interventions such as CIMT, and robot-assisted training for making it more easy for the patient to conduct these kinds of training.

We are actually examining whether BoNT-A therapy prior to NEURO-15 can improve the therapeutic effects for the motor function in patients with upper limb hemiparesis. We included 80 poststroke patients with upper limb hemiparesis whose BRS for hand-fingers were stage III to V and who received NEURO-15 through April 1, 2010, to January 20, 2013, at our affiliated and collaborative hospitals. All the subjects met the following criteria for inclusion:

(1) MAS of ≥1 for finger flexor muscles and/or wrist flexor muscles. (2) BRS for hand-fingers of 3–5 (ability, at least subjectively, to flex all fingers of the affected upper limb in full range of motion). (3) Age at intervention between 18 and 90 years. (4) Time between the onset of stroke and intervention of ≥12 months. (5) A

Table 8.3 Motor function evaluation results before and after combination treatment with BoNT-A and NEURO-15[a]

Evaluation method and outcome measures		Pre-treatment	Post-treatment	*P* value
MAS	Elbow flexor muscle group	1.55 ± 0.82	1.06 ± 0.70	<0.05
	Wrist flexor muscle group	1.51 ± 0.89	0.79 ± 0.74	<0.05
	MCP flexor muscle group	1.52 ± 1.01	0.77 ± 0.81	<0.05
FMA (upper limb)		36.6 ± 12.2	42.5 ± 12.5	<0.05
WMFT	15 Task performance time (seconds)	688.3 ± 406.8	557.0 ± 368.9	<0.05

[a]$N = 67$, evaluation results are all expressed as mean ± SD

single symptomatic stroke lesion confirmed with clinical examination and brain MRI (no bilateral stroke lesions). (6) No marked cognitive impairment. (7) No active physical or mental illness. (8) No recent history of seizure. (9) No documented epileptic discharge on pretreatment electroencephalography. (10) No pathological conditions known to be contraindications for rTMS in the guidelines suggested by Wassermann [8]. In addition, the following patients were excluded from the study: patients with contraindications for intramuscular injection on BoNT-A (e.g., preexisting neuromuscular diseases, bleeding disorders, allergy or hypersensitivity to the product), patients who had received BoNT-A injections previously, and patients with concomitant use of oral antispastic medication.

The examined subjects were divided into two groups: one included 42 patients who received BoNT-A beforehand (mean age: 62.9 ± 10.2 years old, mean time after stroke: 62.0 ± 51.7 months), and the other included 38 patients who did not receive BoNT-A beforehand (mean age: 57.2 ± 15.2 years old, mean time after stroke: 48.0 ± 29.8 months). During the 15-day hospitalization, each subject received 12 treatment sessions consisting of (1) low-frequency (1 Hz) transcranial magnetic stimulation for 40 minutes, (2) tailored occupational therapy for 120 minutes, and (3) self-exercise for 120 minutes. The group with prior administration received an intramuscular injection of BoNT-A before the first treatment session. MAS was used to evaluate the contracture level of the wrist and the finger flexor muscles, while FMA and WMFT were used to evaluate the upper limb function. Each patient was assessed before and after treatment. As a result, a statistically significant improvement in the upper limb function was observed at the time of discharge in both groups ($P < 0.001$) from the time of hospitalization. The amount of change in MAS and FMA of finger flexor muscles in the group with prior administration of BoNT-A improved significantly compared to the group without prior administration ($P < 0.05$).It was demonstrated that prior administration of BoNT-A can improve the therapeutic effect of NEURO by improving the upper limb spasticity [9].

2 Coadministration of Levodopa with rTMS (Naoki Yamada, Wataru Kakuda, and Masahiro Abo)

A. Mechanism of Action of Dopamine

Dopamine is a neurotransmitter that is present in the central nervous system and a precursor to adrenaline and noradrenaline. Neurons that release dopamine are called dopaminergic neurons, and among these there are dopaminergic cell groups called A8, A9, A10 that are considered to be involved in learning and the execution of movements. A8 cell group is located in the retrorubral field (RRF), A9 cell group in the substantia nigra pars compacta (SNc), and the dopaminergic A10 cell group in the ventral tegmetal area (VTA). The VTA forms a part of two dopaminergic pathways through which the nucleus accumbens is connected with the mesolimbic system, and the frontal lobe is connected with the mesocortical system.

The nigrostriatum, which is related to Parkinson's disease, was previously believed to be directly involved in motor control; however, then it was found that motor control is regulated via, e.g., the globus pallidus and substantia nigra pars reticulate [10, 11]. When the dopamine needs of the striatum are depleted due to the degeneration or loss of dopaminergic cells in the substantia nigra pars compacta, then this results in movement disorders that are mainly characterized by akinesis, rigidity, and tremor. When the excitatory input to cells of the direct pathway that arises from the striatum through the D1 receptor is reduced due to dopamine depletion, then these activities decrease, and neural activity of the internal segment of the globus pallidus is enhanced. In addition, when the inhibitory input to cells of the indirect pathway that arises from the striatum through the D2 receptor is reduced, then these activities decrease, and as a result neural activity of the external segment of the globus pallidus is reduced, and neural activity of the subthalamic nucleus and internal segment of the globus pallidus is enhanced. Through these mechanisms, neural activity of the internal segment of the globus pallidus and substantia nigra pars reticulate is enhanced, and as a result the activity of the thalamus and cerebral cortex is suppressed. Moreover, it has been found that the effects of dopamine on the nigrostriatal pathway are also related to the brain's reward system. It is believed that dopamine plays a role in learning to predict which rewards one can expect depending on one's actions.

A reduction in dopamine levels does not only cause motor function adjustment disorders but also greatly affects mental activity and learning function. Depending on the areas that were affected by the stroke these neural pathways can be directly or indirectly impaired, and cause symptoms similar to Parkinson's disease. Therefore, it is important to determine which site was impaired, and to carry out rehabilitation and promote dopamine secretion while taking consideration of emotional functions of the patient such as pleasure and discomfort and expected rewards. However, since the effects of rehabilitation are limited, it is important also to consider a drug therapy that facilitates dopamine secretion.

B. Oral Levodopa + NEURO-15

In 2001, in a double-blind RCT that involved 53 first-ever stroke patients, after daily low-dose levodopa (100 mg) for 3 weeks followed by rehabilitation, motor function was found to have been significantly improved compared to the placebo group [12].

Since orally administered dopamine cannot cross the blood–brain barrier, levodopa was used as a prodrug of dopamine (precursor). Levodopa crosses the blood–brain barrier by making use of the L-amino acid transport mechanism and is decarboxylated in neurons of the central nervous system to form dopamine. However, since after long-term levodopa therapy the effect of levodopa becomes shorter, a phenomenon that is called "wearing off," treatment is generally initiated with small doses of levodopa.

As described above, there are dopaminergic neurons that are profoundly involved in learning and the execution of movements, namely, cell groups A8, A9, and A10.

Through the oral intake of levodopa, the dopamine secretion of these neurons can be supplemented. When dopamine secretion is enhanced, overactive basal ganglia are suppressed, and this in turn suppresses excessive muscle tone and triggers smooth movements. Moreover, since dopaminergic neurons also influence functions of the frontal association area and limbic cortex, they also affect the setting in of motions, and psychophysiological and learning functions. Thus, through the performance of appropriate exercises, and by acting on the limbic system, which is that part of the brain that controls our emotions, autonomic dopamine secretion is promoted, and neural circuits that are involved in motor learning are reinforced.

Focusing on these effects of levodopa, we examined the safety and efficacy of oral intake of levodopa combined with rTMS treatment. In a study five poststroke patients with hemiparesis started oral administration of low-dose levodopa (100 mg) 1 week prior to 2-week hospitalization for NEURO-15 treatment and continued the medication through hospitalization to 4 weeks after discharge. This study was completed without observing any side effects, and a significant improvement in motor function was seen. After 4 weeks when evaluating motor function again this improvement was still sustained or an even greater improvement was observed [13]. We expect that in the future not only levodopa but also other drugs that are more effective and safely increase brain activity will be used in combination with rTMS.

3 Clinical Introduction of Other Stimulation Modalities

Classification of TMS

1) What Are Conventional and Patterned rTMS?

At present the application of rTMS is based on various theories, and depending on the stimulation method rTMS is roughly classified into two types as shown in Fig. 8.2.

Conventional regular rTMS is called “conventional rTMS,” and irregular rTMS is called “patterned rTMS.” Conventional rTMS stimulation is a method in which stimulation is repeated at regular intervals. Stimulation at a frequency of 1 Hz or less is defined as low-frequency rTMS, and 5 Hz and more is defined as high-frequency rTMS. As shown in Fig. 8.3, patterned rTMS includes TBS in which bursts of three pulses are repeated at high frequency (50 Hz), and quadri-pulse stimulation (QPS) [14]. It has been reported that QPS, in which bursts of four pulses are repeated, or changes in the stimulation interval, result in both facilitatory and inhibitory effects that are consistent with the synaptic plasticity response defined in the Bienenstock-Cooper-Munro (BCM) theory [15].

Low-frequency rTMS of conventional rTMS, cTBS of patterned rTMS, and QPS using long stimulus intervals (e.g. 50 ms) result in a prolonged inhibitory effect on output from the corticospinal pathway. On the contrary, high-frequency rTMS using conventional rTMS, iTBS of patterned rTMS (described below), and QPS at short stimulus intervals (e.g. 5 ms) result in a prolonged enhancing effect.

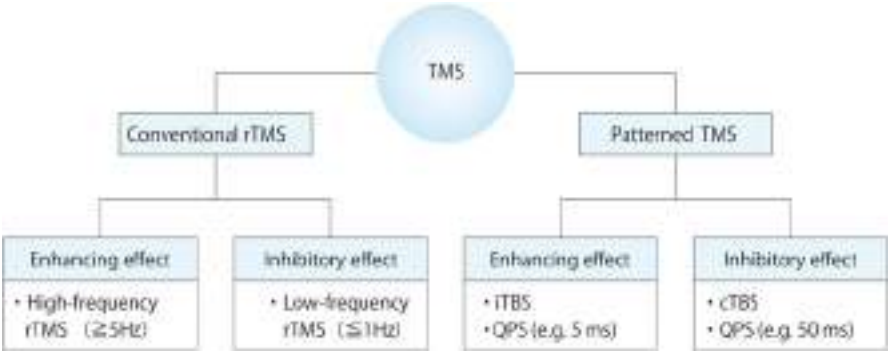

Fig. 8.2 Classification of TMS

2) What Is TBS?

Among various kinds of patterned rTMS, here we describe TBS, the clinical application of which is expected to further increase in the future. Huang et al. [16] reported that TBS can change the excitability of the human cerebral cortex within a short period of time, and in recent years, TBS which previously was only used in animal studies is increasingly also applied in humans, and research on the elucidation of its mechanism of action has advanced. The stimulation intensity used for TBS is only weak, namely, 80 % of the motor threshold of voluntary contraction. TBS consists of 3-pulse TMS trains at 50 Hz (TMS consisting of three pulses at intervals of 20 ms) that are repeated at regular intervals, in total 300–600 pulses. TBS stimulation methods include continuous TBS (cTBS), intermittent TBS (iTBS), and intermediate TBS (imTBS) (Fig. 8.3) [14].

Huang et al. reported that when using this method a short stimulation duration of only 40 seconds (cTBS) was sufficient to reduce the excitability of the cerebral cortex for approximately 60 minutes. In this report it is pointed out that conversely at the same intensity and same number of 600 pulses it is possible to enhance the excitability of the primary motor area when slightly changing these stimulation conditions. More specifically, the excitability of the cerebral cortex was enhanced when 3-pulse TMS at 50 Hz is repeated as 2-second train at frequency of 5 Hz every 10 seconds (total of 600 pulses). Reportedly with this method the excitability of the human cerebral cortex could be enhanced or reduced after only extremely short stimulation duration of 20–190 seconds, and the clinical application of this rTMS stimulation method is believed to hold promise for the future.

We then also conducted a pilot study which examined how TBS in combination with the intensive occupational therapy can improve the motor function in post-stroke patients with upper limb hemiparesis. We included 25 stroke patients in the chronic phase with upper limb hemiparesis (mean age: 62.2 ± 12.6 years old, mean time after stroke: 71.8 ± 63.6 months) who received inpatient treatment at Shimizu Hospital, one of our affiliated hospitals, for 15 days during the period from February 2 to December 21, 2013. Their BRS for upper limb and hand-fingers were III or more, and they had not received botulism in combination.

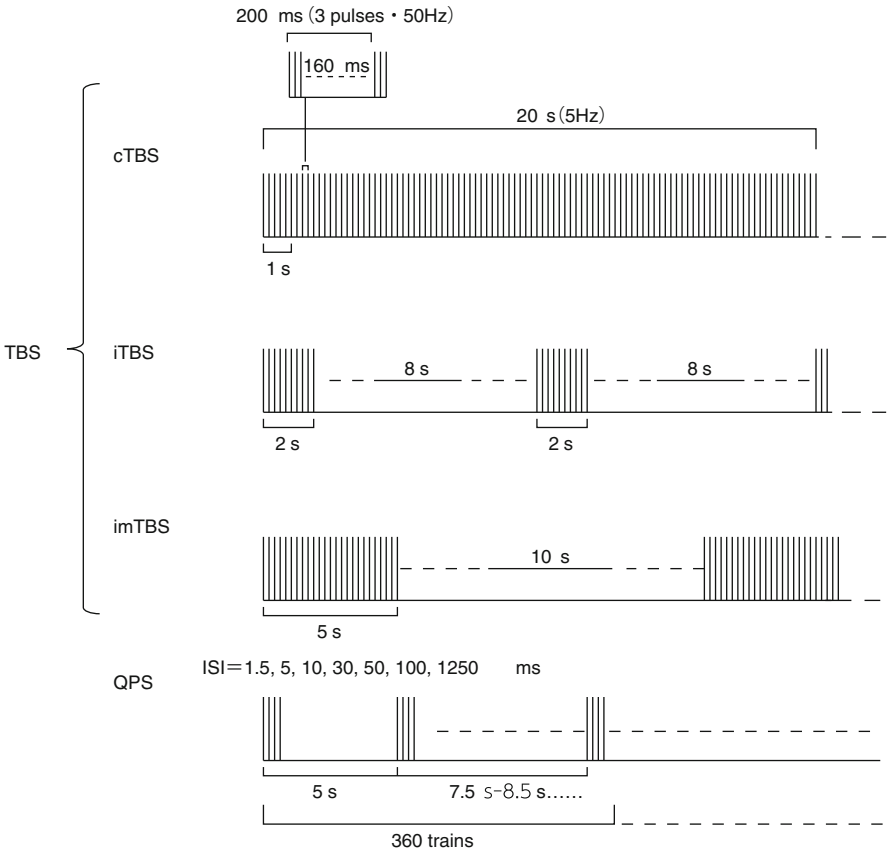

Fig. 8.3 Schematic diagram of patterned TMS

Each patient received a 15-day treatment session consisting of (1) transcranial stimulation to the nonlesional hemisphere with 2400 pulses (80 % of the motor threshold of the first dorsal interosseous muscles at rest) via cTBS, which continuously provides three repeated stimulations of 50 Hz at 5 Hz, (2) tailored occupational therapy for 120 minutes, and (3) self-exercise for 120 minutes. The upper limb function was evaluated twice using FMA and WMFT on the day of hospitalization and the day before discharge. The treatment and the study were approved as a clinical study by the Ethical Review Board at Shimizu Hospital, and the doctors obtained written consent from their patients.

This treatment protocol was accomplished without any adverse events in all the subjects. The change in FMA and WMFT before and after treatment suggested the improvement of the upper limb motor function. While it has already been reported that conducting NEURO-15 in poststroke patients with hemiparesis can improve the upper limb function, a similar result was obtained when conducting TBS in this study. One of the advantages of TBS is that the stimulation lasts only 3 minutes and both patient's and medical staff's burden can be reduced. Future studies on the

long-run effect are required, however; we believe that the combination protocol of theta burst consecutive magnetic stimulation, which is our idea, and intensive occupational therapy can be a new treatment for upper limb hemiparesis in poststroke patients [17].

B. What Is Bihemispheric rTMS?

Here we present previous research in which both conventional low-frequency and high-frequency rTMS were applied to both of the hemispheres. When rTMS is used for therapeutic purposes, methods that directly apply high-frequency rTMS to the affected hemisphere could take in a compensatory role, and methods that apply low-frequency rTMS to the nonlesional hemisphere weaken the interhemispheric inhibition of the affected hemisphere, thus trying to indirectly activate sites that can compensate for lost functions by releasing them from interhemispheric inhibition.

Although various studies have been conducted to examine the merits and demerits of these two approaches, it is still not clear which is superior; both high-frequency rTMS and low-frequency rTMS have merits and demerits. Regardless of which approach is used, the application of rTMS induces neuroplasticity, and promotes the functional recovery of the paralyzed hand of stroke patients. On the grounds of the interhemispheric competition model of poststroke patients, we believe that by applying high-frequency rTMS to the affected hemisphere in addition to low-frequency rTMS to the nonlesional hemisphere greater improvement might be achieved than with unilateral rTMS alone.

There is no report on the combined application of high-frequency and low-frequency rTMS for therapeutic purposes in poststroke patients in combination with intensive rehabilitation on consecutive days. Therefore, we present here a research paper in which we determined the safety of 10-Hz high-frequency rTMS and its efficacy in the treatment of poststroke patients with upper limb hemiparesis when applied to the affected hemisphere in addition to NEURO-15, which is a combination of low-frequency rTMS and intensive rehabilitation and was used as basic treatment [18].

This study included eight poststroke patients with upper limb hemiparesis who were hospitalized at our department between September 17 and December 17 in 2011 and received high-frequency rTMS (10 Hz) to the affected hemisphere + NEURO-15, and whose BRS were stage III to V for both upper limb and hand-finger (mean age: 62.8 ± 4.9 years old, mean time after stroke: 84.3 ± 87.2 months, type of stroke: four intracerebral hemorrhage, four cerebral infarction). The eligibility criteria were similar to those for NEURO-15 shown in Chap. 2 (p. 21).

All eight patients were treated as follows: (i) the affected and unaffected hemispheres were stimulated alternatively with a total of 4000 pulses/day, namely, 2000 pulses each of low-frequency (1 Hz) stimulation to the unaffected hemisphere and high-frequency (10-Hz) stimulation to the affected hemisphere (10 Hz for

Table 8.4 Hospitalization schedule for bihemispheric rTMS[a]

	Day 1	Day 2	Day 3–7	Day 8	Day 10–13	Day 14	Day 15
Morning	Admission		Bihemispheric rTMS (40 minutes)		Bihemispheric rTMS (40 minutes)	Bihemispheric rTMS (40 minutes)	Discharge
		Low-freq. rTMS (20 minutes)	One-to-one OT (80 minutes)	Low-freq. rTMS (20 minutes)	One-to-one OT (80 minutes)	One-to-one OT (40 minutes)	
		Self-exercise (60 minutes)	Self-exercise (60 minutes)	Self-exercise (60 minutes)	Self-exercise (60 minutes)	Self-exercise (60 minutes)	
Afternoon	Evaluation of upper limb function	One-to-one OT (60 minutes)	One-to-one OT (40 minutes)	One-to-one OT (60 minutes)	One-to-one OT (40 minutes)	Evaluation of upper limb function	
		Self-exercise (60 minutes)	Self-exercise (60 minutes)	Self-exercise (60 minutes)	Self-exercise (60 minutes)		

[a]Complete rest on Day 9

5 seconds, followed by 1 Hz for 50 seconds, and this cycle was repeated 40 times). Moreover, during the 15-day hospitalization period daily treatment sessions consisting of (ii) one-to-one OT 6 units/day (40 minutes × 3) and (iii) self-exercise 120 minutes/day were conducted. The hospitalization schedule of this therapy is shown in Table 8.4.

The stimulation site and the intensity of low-frequency rTMS were determined on the day of admission. The stimulation site was set as the hand-finger areas in the primary motor cortex of the unaffected hemisphere, and the intensity of stimulation was set at 90 % of the minimum stimulation intensity that induces motor evoked potentials (MEPs) of maximum peak-to-peak amplitude in the abductor pollicis brevis muscle of the nonparalyzed upper limb. Low-frequency rTMS was applied by use of MagPro R30 and figure-8 coil (both manufactured by MagVenture). Actual treatment by bihemispheric rTMS in a clinical setting is shown in Fig. 8.4. Moreover, motor function of the upper limb was evaluated by use of FMA, WMFT, and MAS on the day of admission and discharge.

As a result, this treatment protocol was completed in all patients without observing any adverse events. Changes in FMA, WMFT, and MAS before and after treatment suggested an improvement in motor function of the upper limb in all patients (Table 8.5). Moreover, a statistically significant improvement was observed in the results of FMA, WMFT, and MAS before and after treatment (Table 8.6).

In this treatment, the first and strong approach in which consecutive rTMS is given alternatively to both hemispheres for 11 days in combination with intensive rehabilitation can lead to a long-term effect of motor function improvement and functional reorganization in a use-dependent manner. We believe that simultaneous stimulation with low- and high-frequency rTMS combined with intensive OT may become a new therapeutic approach for the treatment of poststroke upper limb hemiparesis [18].

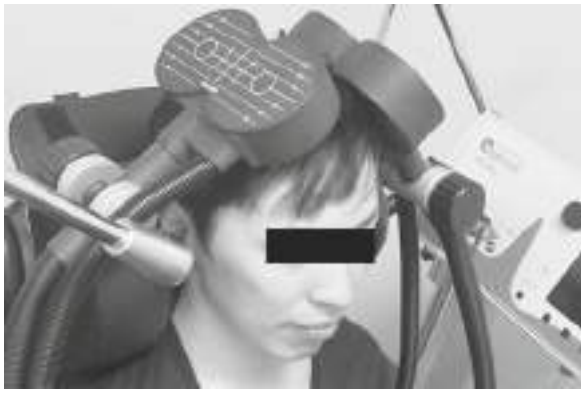

Fig. 8.4 Bihemispheric rTMS in a clinical setting

Table 8.5 Motor function evaluation results

Patient no.	FMA for upper limb		WMFT				MAS					
			Performance time of 15 tasks (seconds)		FAS		Finger flexor muscle group		Wrist flexor muscle group		Elbow flexor muscle group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
1	46	57	573.6	329.1	37	47	3	1	1.5	0	2	1.5
2	37	38	884.2	388.8	31	45	2	1	1.5	0	1.5	1
3	47	56	59.7	39.8	48	59	1.5	1	1.5	0	0	0
4	54	63	197.6	176.5	57	66	1.5	0	1.5	1	1	0
5	49	52	1213.0	977.4	28	31	1	0	2	1.5	1	0
6	25	39	782.3	659.9	33	35	1.5	1	1.5	0	1.5	1
7	27	41	857.0	135.2	32	46	1	0	1	0	1	1
8	44	53	522.49	186.81	41	49	1	0	1	0	1.5	1

Table 8.6 Statistical data of the results of motor function evaluation[a]

Evaluation method	Outcome measure	Pre-treatment	Post-treatment	*P* value
BRS	Upper limb	3.4 ± 0.7	3.5 ± 0.8	N.S
	Hand-fingers	4.0 ± 0.5	4.4 ± 0.7	N.S
MAS	Elbow flexor muscle group	1.2 ± 0.6	0.7 ± 0.6	<0.05
	Wrist flexor muscle group	1.4 ± 0.3	0.3 ± 0.6	<0.05
	Finger flexor muscle group	1.6 ± 0.7	0.5 ± 0.5	<0.05
	Total score	41.1 ± 10.5	49.9 ± 9.4	<0.05
FMA	Evaluation item A	24.8 ± 6.1	28.0 ± 4.9	N.S
	Evaluation item B	5.1 ± 1.7	7.8 ± 1.5	<0.05
	Evaluation item C	8.6 ± 3.5	11.1 ± 3.7	<0.05
	Evaluation item D	2.6 ± 1.6	3.0 ± 1.7	N.S
WMFT	Performance time for 15 tasks (seconds)	636.2 ± 379.1	361.7 ± 313.9	<0.05
	Natural logarithm of mean performance time	3.5 ± 1.0	2.8 ± 1.0	<0.05

[a]All evaluation results are expressed as mean ± SD

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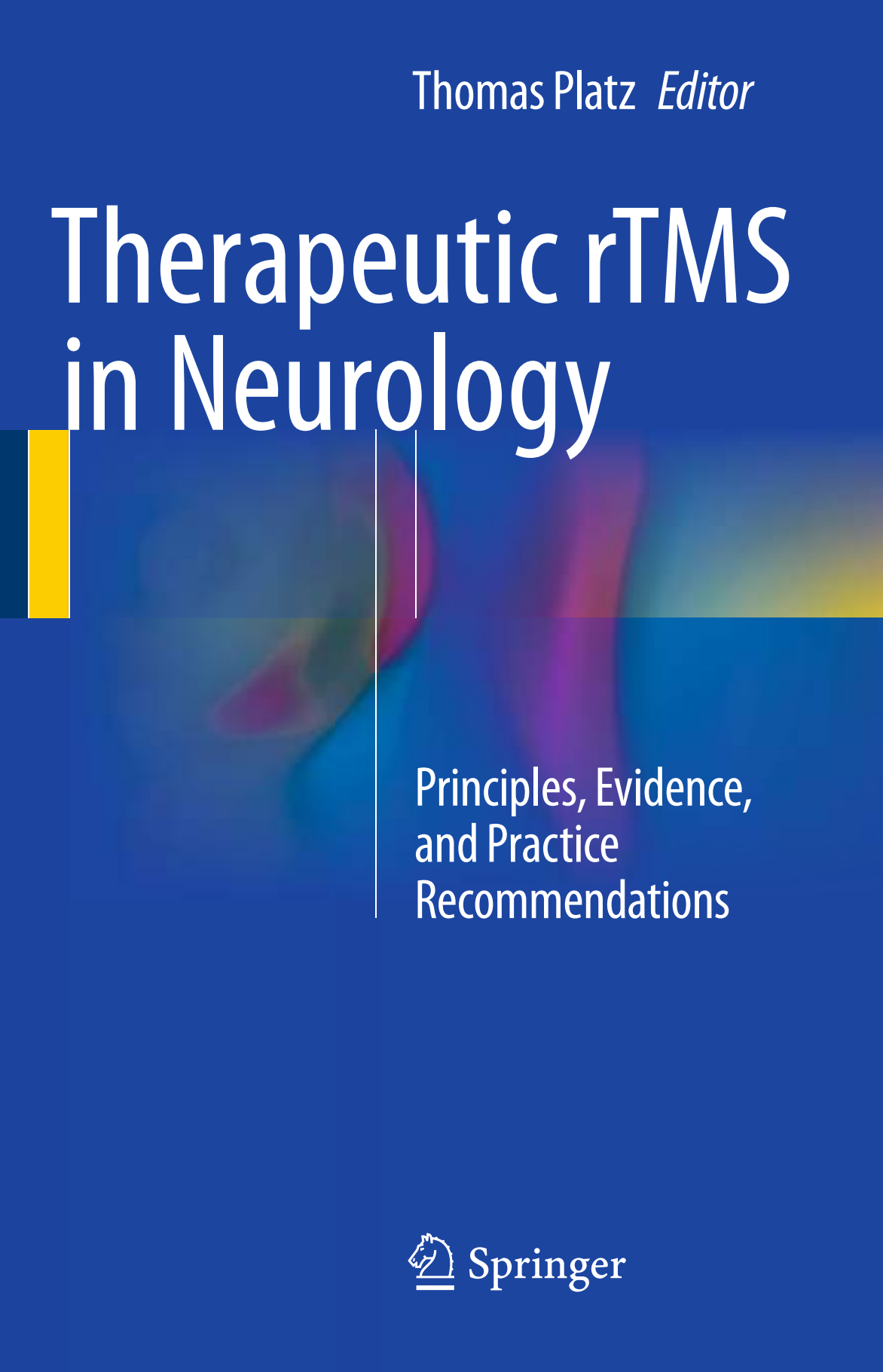
Thomas Platz *Editor*

Therapeutic rTMS in Neurology

Principles, Evidence, and Practice Recommendations



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Therapeutic rTMS in Neurology

Thomas Platz
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Therapeutic rTMS in Neurology

Principles, Evidence, and Practice Recommendations

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Preface

Therapeutic repetitive transcranial magnetic stimulation (rTMS) in clinical neurology is an emerging option to treat various neurological conditions. Many issues need to be resolved for each condition treated and protocols developed with optimized effectiveness taking individual subject characteristics into account. And yet, the clinical benefits that can be achieved are at times remarkable and favor the clinical application of rTMS therapy.

This book is a comprehensive reference on therapeutic rTMS that documents the current status in the field. While introductory chapters cover the neurophysiology of rTMS and present imaging information about its mechanisms of action, the main focus of this book is the clinical applications of rTMS that have been tested to date. These include treatment of paresis, aphasia, and visual neglect in stroke patients, therapy for motor impairment in Parkinson's disease, and applications for tinnitus and neuropathic pain. Based on the available clinical evidence (RCTs, meta-analyses, and systematic reviews), combined with the personal experience of experts in the field, a clinically oriented best evidence synthesis is provided for each therapeutic application, together with a clear description of rTMS algorithms that generate clinical benefits in the target domain.

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Contents

Neurophysiology of rTMS: Important Caveats When Interpreting the Results of Therapeutic Interventions

1

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Abstract

Transcranial magnetic stimulation (TMS) is a safe and non-invasive method of stimulating neurons in intact humans. TMS uses electromagnetic induction to induce weak electric currents in the brain. There is good evidence that repetitive application of TMS (repetitive TMS, rTMS) can produce after-effects, offering potential for clinical application in variety of neurological and psychiatric diseases. Although the mechanisms of this after-effect are not fully understood, because of its similarity to synaptic plasticity in animals, it is generally assumed that rTMS-induced effects may closely relate to synaptic plasticity, such as long-term potentiation (LTP) or depression (LTD). Therefore, the term LTP- or LTD-like is frequently used to describe the changes observed after rTMS. It has yet, however, to be demonstrated that the site of rTMS-induced changes is the synapse. Furthermore, the response to rTMS is highly variable. A number of factors have been identified that could contribute to this, but none of them accounts for a large proportion of the effect. This unavoidable variability of rTMS hampers attempts to assess treatment effectiveness. One potential approach to dealing with this problem is to find strong predictors of the response to rTMS so that parameters of stimulation could be optimized on an individual basis. Another would be to invent new non-invasive stimulation protocols that have more consistent effects in all individuals. Variability in response to rTMS need not be seen as a weakness of this method but a great opportunity to gain further insight into individual differences in the awake human brain.

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1.1 Synaptic Plasticity

Synaptic plasticity is the most widely studied physiological model of memory formation, learning and recovery after brain damage (Cooke and Bliss 2006) and is an attractive candidate model for information storage in the brain.

It refers to activity-dependent increases or decreases of synaptic efficiency, such as long-term potentiation (LTP) or depression (LTD). It is well established that LTP and LTD can be experimentally achieved using a number of different induction protocols especially in hippocampal slice (Cooke and Bliss 2006). For example, LTP is induced by tetanic electrical stimulation (e.g. typically a train of 50–100 stimuli at above 100 Hz) (Bliss and Collingridge 1993), while LTD can be obtained by low-frequency stimulation (>900 stimuli at 0.5–3 Hz) (Dudek and Bear 1992). LTP can be also induced by theta-burst stimulation (TBS) in which a high-frequency burst of stimuli (10–20 stimuli at above 100 Hz) is repeated at theta frequency (usually 5 Hz) . Another example is spike timing-dependent plasticity (STDP). Here precise timing of activation of pre- and postsynaptic neurons determines direction of synaptic plasticity (Dan and Poo 2006). It is important to note that LTP and LTD have been extensively studied in well-defined pathways or even at a single synaptic connection between pre- and postsynaptic neurons (see below).

Although there are several different forms of LTP and LTD, in general, Ca^{2+} concentration in postsynaptic neurons is likely to play a key role in determining the direction and extent of the effect. Some forms of LTP and LTD, for example, require synaptic activation of N-methyl-D-aspartate receptors (NMDAR) during postsynaptic depolarization, leading to the influx of Ca^{2+} through the NMDAR channel and a change in Ca^{2+} within the dendritic spine (Malenka and Bear 2004). Whether the final effect is LTP or LTD is, at least in part, caused by the subsequent signalling cascade after Ca^{2+} influx. Activation of calcium-/calmodulin-dependent kinase II (CaMKII) or the cyclic adenosine monophosphate (cAMP)-dependent pathways initiates LTP expression, while calcineurin and protein phosphatase 1 are involved in LTD. However, a number of other factors influence LTP or LTD induction. These include prior history of synaptic plasticity (metaplasticity mechanisms), NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits, catecholamines, γ-aminobutyric acid (GABA), acetylcholine, cytokines and hormones (Abraham 2008). Therefore, none of these can simply explain the difference in induction of LTP and LTD; instead synaptic plasticity is likely to be determined by a complicated interaction between them.

1.2 Repetitive Transcranial Magnetic Stimulation and Synaptic Plasticity

It is currently possible to stimulate intact human brain by means of repetitive application of single pulse transcranial magnetic stimulation (so-called repetitive TMS, rTMS). In principle, TMS uses electromagnetic induction to induce weak electric currents in the brain (Fig. 1.1a). A large pulse of current in the external stimulating

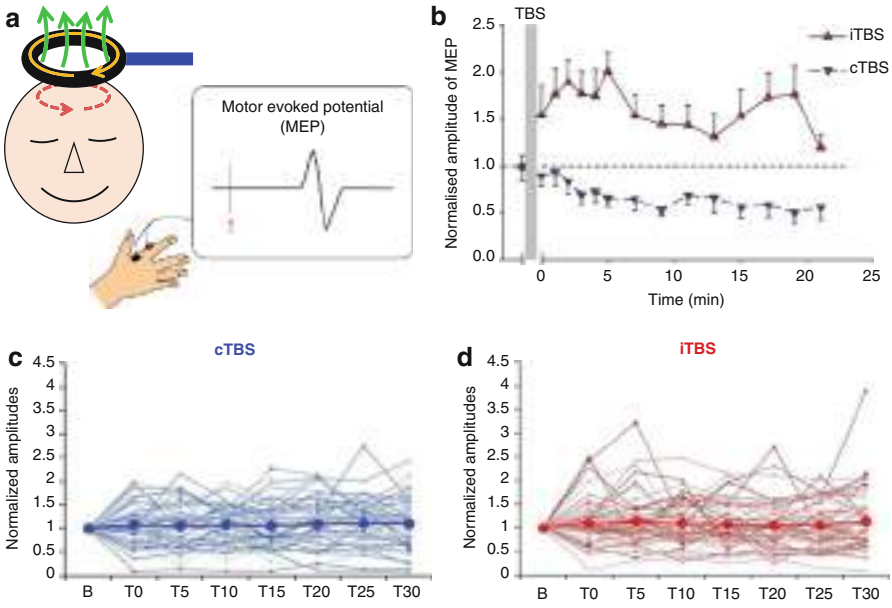

Fig. 1.1 (**a**) Basics of TMS. A large pulse of current in the external stimulating coil generates a rapidly changing magnetic field that rises to, and falls from, 1 T or more within 1 ms, and this field can penetrate the scalp and skull with little impedance. Accordingly, the electrical field it induces causes an eddy current to flow in the area of the brain beneath the coil, resulting in depolarization of axons in the cortex. If TMS is applied over the primary motor cortex, it can induce a small twitch in the target muscle, so-called motor evoked potential (MEP). (**b**) Mean effects of theta-burst stimulation (TBS) on MEP amplitudes in nine individuals. In these people, intermittent TBS (iTBS) produces lasting increase, while continuous TBS (cTBS) induces lasting decrease of MEP sizes compared to baseline. Modified from Huang et al. (2005) (**c**, **d**) Effects of TBS are highly variable when larger number of participants are analysed. Data plotted from 52 healthy young subjects (Modified from Hamada et al. (2013))

coil generates a rapidly changing magnetic field that rises to, and falls from, 1 T or more within 1 ms, and this field can penetrate the scalp and skull with little impedance. Accordingly, the electrical field it induces causes an eddy current to flow in the area of the brain beneath the coil. When a sufficient intensity of stimulation is used, the induced current which lasts for about 200 μs can depolarize the axons of neurons in the cortex. Thus, the stimulus induced by TMS is comparable to conventional electrical stimulation as in slice preparations. However, it is important to note that TMS activates a number of excitatory and inhibitory neurons underneath the coil simultaneously. Thus, the effects of rTMS reflect the sum of its effects on excitatory and inhibitory neurons.

There is good evidence that rTMS can produce after-effects on the brain, offering potential for clinical application in variety of neurological and psychiatric diseases (Chap. 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12). These after-effects outlast the stimulation period and are usually described as “LTP-/LTD-like” plasticity depending on whether the overall effect is an increase or decrease in cortical excitability, as

indexed by motor evoked potential (MEP) amplitudes (Fig. 1.1a). There are number of similarities to synaptic plasticity in animal preparations (Ziemann et al. 2008). First, the effects are likely to take place at the cortex because spinal excitability is not altered by the interventions. As with many demonstrations of synaptic plasticity in animals, in humans, the effects often evolve rapidly, yet are reversible, lasting for 30–60 min. Furthermore, it has been shown that NMDAR antagonists block the plasticity induced by some rTMS protocols (Stefan et al. 2002; Wolters et al. 2003; Huang et al. 2007). Thus, at least some forms of plasticity induced by rTMS are likely to be NMDA dependent. Synaptic effects of rTMS are also compatible with its interaction with behavioural learning (Ziemann and Siebner 2008) or recovery after stroke (Di Pino et al. 2014; Grefkes and Ward 2014). Thus, forms of rTMS can suppress (Muellbacher et al. 2001; Baraduc et al. 2004; Kang et al. 2011) or facilitate learning (Jung and Ziemann 2009). Given that synaptic plasticity is a likely substrate for learning, it has been implicitly assumed that such interference may be caused via effects on synaptic plasticity.

As in animal experiments, several protocols have been reported to induce LTP- and LTD-like plasticity (Table 1.1). Conventional rTMS refers to rTMS at fixed frequency: high-frequency rTMS at 5 Hz or higher transiently increases cortical excitability (i.e. LTP-like), while stimulation at 1 Hz decreases cortical excitability (LTD-like) (see also BOX1). Patterned rTMS involves more complex protocols, the most common of which is theta-burst stimulation (TBS) which consists of a burst of 3 pulses at 50 Hz, repeated at 5 Hz, as in slice preparations (Huang et al. 2005) (Fig. 1.1b). Another example is quadripulse stimulation (QPS) in which a burst of 4 pulses is repeated at a rate of 0.2 Hz. Depending on the interval within 4 pulses, QPS is capable of inducing either LTP- or LTD-like plasticity (Hamada et al. 2008). Paired associative stimulation (PAS) is another commonly used protocol in which electrical stimulation of peripheral nerve is repeatedly paired with TMS over the contralateral primary motor cortex. The effective median nerve-TMS interval at approx. 21.5–25 ms or 10 ms is thought to reflect the time window for development of spike timing-dependent (STDP) plasticity at cortical synapses activated by median nerve input and TMS (Stefan et al. 2000; Wolters et al. 2003). LTD-like effects are seen when the TMS-verve interval is 10 ms, whereas LTP-like effects occur at 21.5–25 ms.

Table 1.1 Summary of rTMS protocol for LTP- and LTD-like plasticity induction

Protocol	LTP-like plasticity	LTD-like plasticity
Conventional rTMS	High frequency, >5 Hz	Low frequency, 0.2–1 Hz
Patterned rTMS		
TBS	Intermittent TBS	Continuous TBS
QPS	QPS-5	QPS-50
PAS	PAS25	PAS10

TBS theta-burst stimulation, *QPS* quadripulse stimulation, *PAS* paired associative stimulation (PAS)

Although the effects induced by rTMS (see above) are consistent with modifications of synaptic plasticity, we still lack definitive proof of their origin. Similarities such as NMDA dependency do not necessarily imply common mechanisms. In addition, unlike slice experiments in which one pathway or connection is investigated, the plasticity of rTMS results from the sum of changes in a number of excitatory and inhibitory connections (Di Lazzaro and Rothwell 2014). In fact, it is possible that synaptic plasticity evoked by rTMS in one pathway may not be the same as in other pathways (Dan and Poo 2006; Feldman 2009; Collingridge et al. 2010). Even in animal experiments, LTD is easily induced in excitatory synapses of distal dendrites, while proximal synapses are prone to LTP (Letzkus et al. 2006). Furthermore, there are different types of STDP at inhibitory synapses (Feldman 2012). Another puzzling point is that it is often difficult to induce synaptic plasticity in neocortex of adult or behaving animals (Hess and Donoghue 1994; Racine et al. 1994a, b; Hess et al. 1996; Chapman et al. 1998; Trepel and Racine 1998), while it seems to be very easy to produce plasticity by rTMS in adult human brain. In behaving animals, the LTP protocol usually requires stimulation for days (Trepel and Racine 1998) or even application of a GABA-antagonist to achieve disinhibitory states (Hess et al. 1994). In contrast, cTBS using rTMS induces LTD-like plasticity in a few minutes in adult human brain (Huang et al. 2005). These data raise the question whether synaptic plasticity is solely and exclusively responsible for what we observe in intact humans. Taken together, since after-effects of rTMS result from mixture of distinct (either LTP or LTD) changes in (presumably) a number of different synaptic connections, it may be an oversimplification to describe the after-effects of rTMS as LTP or LTD-like plasticity exclusively based on MEP changes.

1.3 Variability in Response to rTMS

Ever since the introduction of rTMS (Pascual-Leone et al. 1994), it has been well recognized that the response to rTMS is highly variable. This was firstly reported in a small number of subjects with conventional rTMS (Maeda et al. 2000). Subsequent studies in larger numbers of healthy subjects have confirmed that there is a considerable variability in response to any rTMS protocol (Table 1.1) (Müller-Dahlhaus et al. 2008; Hamada et al. 2013; López-Alonso et al. 2014; Wiethoff et al. 2014). In general, the probability of producing the "expected" response may be as low as 50 %, at least as measured by effects on the MEP based on the recent studies with relatively large number of subjects (Figs. 1.1c, d, and 1.2) (see also (Horvath et al. 2014)). A number of factors have been identified to explain this variability, such as age, gender, time of day, physical activity, prior history of synaptic activity, state of cortex, interneuron networks, or even genetics (Ridding and Ziemann 2010). However, none of them accounts for a large proportion of the variation which thus must be regarded as multifactorial. It may be possible to simplify the sources of variability into two groups: intrinsic and extrinsic. Intrinsic variability may relate to factors that are impossible to modify, such as age, gender and genetics. Extrinsic variability is potentially controllable and includes factors such as state of cortex,

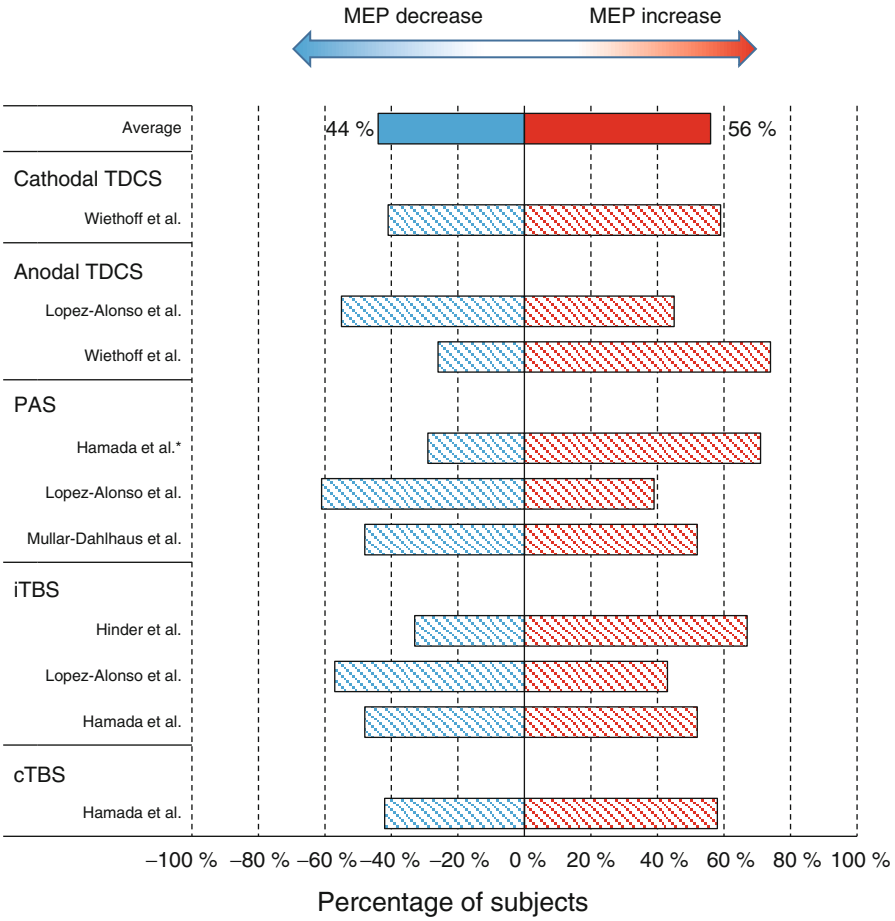

Fig. 1.2 Summary of response profile of each protocol. The bar indicates the percentage of subjects who showed MEP increase or decrease in each study. Note that this is not a meta-analysis and the studies were chosen from recent studies. This is because these include a relatively large number of subjects (more than 25 subjects) compared with the studies previously reported (see also Horvath et al. 2014). * unpublished data

prior history of synaptic activity, time of day, physical activity, detection of the motor hotspot, the attention level of subjects in a long experiment, etc. For example, some evidence suggests target muscle activity prior to or during rTMS intervention affects response variability. It might be possible to minimize this by a short period of complete EMG silence in target muscle prior to delivering rTMS. However, it is difficult to define a true "rest" condition. Even though participants may maintain complete silence in a target muscle, this does not guarantee that this is true of the whole motor system. In fact, even in a target muscle at rest, motor threshold can be modified when subjects change the focus of their attention (Gandevia and Rothwell 1987). This implies that the resting condition may vary depending on unavoidable

fluctuations of neuronal states including attention, and thus any measure related to rest (e.g. resting motor threshold or MEP at rest) may be ill defined. Finally, it should be remembered that variation in response to rTMS may be due to variation in the ability of the test stimulus to pick up the effects. This could reflect, for example, interindividual variability in interneuron networks involved in the MEP.

Although there are problems in using MEP measurements to detect effects of rTMS, the advantage is that they provide an objective and useful way to measure cortical excitability. Apart from MEP, EEG responses to TMS (transcranial evoked potential, TEP) are a second objective read out of TMS (Massimini et al. 2005; Premoli et al. 2014). The advantage of TEP is that it is available, in principle, to any area of the brain, in contrast to the MEP which can only obtained by TMS over the primary motor cortex. However, there are no studies of range of variation in TEP measures after rTMS in different individuals.

1.4 Effects of rTMS on Behaviour

There is a good evidence that rTMS improves or facilitates the function of certain areas after brain damage or dysfunction. In fact, many clinical trials have reported favourable effects on symptoms in various neurological and psychiatric diseases, such as stroke, depression, Parkinson's disease, pain, etc (Lefaucheur et al. 2014). However, the beneficial effects of rTMS are variable, and the results of these trials are inconsistent. The question is why does this happen?

As already mentioned, we know that the effects of rTMS on MEP excitability are highly variable, but it is not yet clear whether variability in MEPs translates directly into variability in behavioural effect. It is often tacitly accepted that this relationship exists since we select for therapy those protocols that have the "desired" effect on MEPs. However, it may be too simplistic assumption, and therefore, it is worthwhile to know whether the response to rTMS measured using MEPs predicts either (a) a person's intrinsic ability to learn a certain task and/or (b) the effectiveness of an rTMS protocol to enhance a person's performance in a task. For the first point, there is some evidence that MEP changes produced by rTMS do not correlate motor learning rate (Li Voti et al. 2011). The answer may be more positive for the second point. Kang et al (2011) found a negative correlation between rTMS effects on MEPs and the effects of the same rTMS protocol on motor learning (Kang et al. 2011). However, the number of subjects was small, and more information is required to answer the question with certainty. Finally, it may be important to note that the MEP only reflects activity in the large diameter axons of the pyramidal tract. These represent only about 2 % of the total tract. Thus, it is possible that at least some effects of rTMS on behaviour result from activity in other components of the tract or even activity in other tracts such as the rubulospinal, reticulospinal, cortico-cortical and cortico-subcortical pathways (Lemon 2008). In this context, it is interesting to note that MEP changes in the corticospinal system may not correlate with changes in other pathways. Thus, application of an inhibitory rTMS protocol (QPS) over left primary motor cortex (M1) reduced MEPs evoked from left M1, but did not change interhemispheric

(cortico-cortical) inhibition from left to right M1 (Tsutsumi et al. 2014), suggesting that effects on cortico-cortical and corticospinal pathways differ. Future studies are required in order to predict the effects of rTMS in a clinical setting.

Conclusions

Synaptic plasticity may be involved in some of the after-effects of rTMS, but it should be noted that the outcome is due to a mixture of effects on many different synapses. Thus, the concept that a protocol will cause LTP- or LTD-like plasticity at a particular set of glutamatergic synapses may be oversimplified. This mixture of effects may partially explain why the response to rTMS, measured using either MEPs or behaviour, is highly variable. Although evidence supports the potential efficiency of rTMS in clinical settings, it is still challenging to predict the response to rTMS in any one individual.

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Cellular and Molecular Mechanisms of rTMS-induced Neural Plasticity

2

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Abstract

Despite its increasing use in clinical practice, our knowledge on the cellular and molecular mechanisms of repetitive transcranial magnetic stimulation (rTMS) remains limited. Yet, work from the past years has provided important new insights into how TMS excites neural tissue and induces neural plasticity. Emerging evidence suggests that rTMS may act on inhibitory and excitatory networks to induce the structural, functional and molecular remodeling of neuronal networks. Likewise, rTMS-mediated changes in gene expression profiles and neuromodulatory transmitter systems have been reported. Together, these studies confirm that rTMS induces plasticity in cortical brain regions. They indicate that repetitive magnetic stimulation interferes with the ability of neurons to express distinct forms of plasticity beyond the stimulation period. Hence, a biologically driven attempt to improve the use of rTMS in clinical practice has started to emerge. In this chapter we aim at providing a concise review on the current knowledge of rTMS-induced cellular and molecular mechanisms relevant for neural plasticity.

2.1 Introduction

The ability of the brain to adapt to external and internal stimuli with structural, functional, and molecular changes is considered fundamental for a variety of physiological processes, such as circuit formation, learning and memory, and aging. This

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unique property of the central nervous system is termed *neural plasticity*. It is controlled by an intricate crosstalk between neurons and other cell types in the brain, e.g., glial, endothelial, and immune cells (Fig. 2.1a).

While a wealth of information has been acquired on the cellular and molecular mechanisms of various forms of plasticity under physiological conditions, the interplay between distinct forms of plasticity (e.g., Hebbian plasticity, homeostatic plasticity, metaplasticity; see Table 2.1) and their role for neurological and psychiatric diseases remains not well understood (Maggio and Vlachos 2014). Recent evidence suggests that the ability of neurons to express plasticity may change and/or plasticity mechanisms may be recruited in a nonspecific manner under pathological conditions (Hulme and Jones 2013). It has become clear that an impairment of plasticity cannot be simply interpreted as detrimental under pathological conditions, since a reduction in the ability of neurons to express plasticity may protect the brain from "maladaptive changes", which promote the development of disease-related complications such as epilepsy, pain, or memory dysfunction (e.g., Ferguson et al. 2012; Leuner and Shors 2013; Moxon et al. 2014; Nava and Röder 2011; Papa et al. 2014; Swann and Rho 2014; Winkelmann et al. 2014; Zenonos and Richardson 2014). Thus, with a better understanding on the role of neural plasticity under pathological conditions, novel therapeutic approaches could be designed to promote, block, or shift the balance between distinct forms of plasticity in specific brain regions and at diverse stages of pathological brain conditions (Maggio and Vlachos 2014).

Repetitive transcranial magnetic stimulation (rTMS) represents an interesting diagnostic and therapeutic tool in this context. Although our understanding on the cellular and molecular mechanisms underlying rTMS-based therapies remains limited (Müller-Dahlhaus and Vlachos 2013), it has been demonstrated that repetitive magnetic stimulation (rMS) is capable of recruiting plasticity-related mechanisms in neural tissue.

2.2 The Effects of rTMS During Stimulation

Using computational approaches to estimate cortical electric fields induced by TMS in combination with simulations of the effects of electric fields on neurons, some insights into TMS effects on neural tissue have been gained (e.g., Basser 1994; Opitz et al. 2011; Rotem and Moses 2008; Rusu et al. 2014). Nevertheless, it has remained largely unknown how TMS affects individual neurons within distinct cortical networks (Dayan et al. 2013).

A major limitation in this field of research has been the challenge to record from individual neurons during stimulation, due to the strong electromagnetic field induced by TMS. Recent technical advances, however, have made it possible to assess neural activity during stimulation using electrophysiological (Muller et al. 2014; Pashut et al. 2014) or functional optical imaging techniques (Kozyrev et al. 2014). These studies provide experimental evidence that single-pulse magnetic

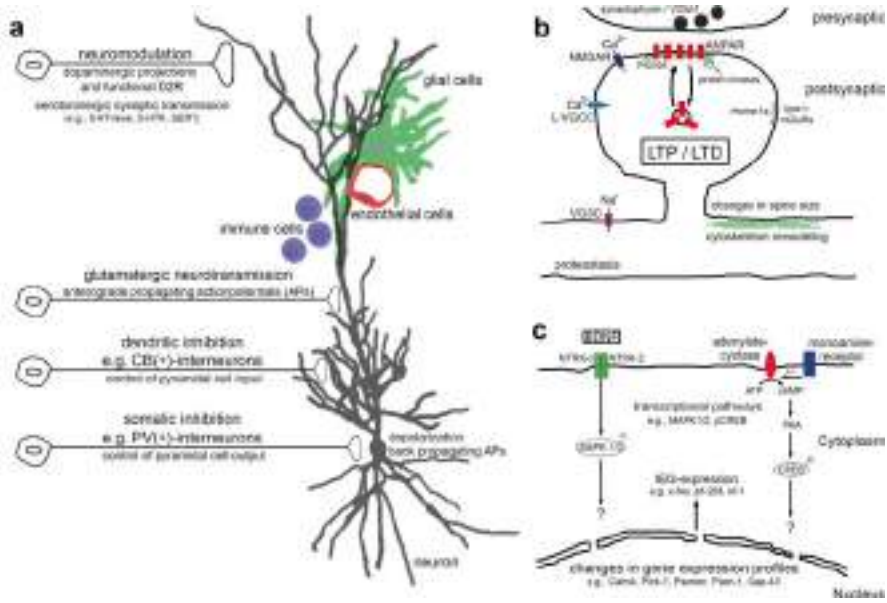

Fig. 2.1 Cellular and molecular effects of repetitive transcranial magnetic stimulation (rTMS) relevant to neural plasticity. (**a**) Schematic illustrating the effects of rTMS on neural tissue. While experimental evidence has been provided that single-pulse TMS can elicit action potentials, the role of structural and functional properties of distinct neurons and local circuitries (e.g., recurrent networks, feed-forward, and feed-back inhibition) remains not well understood. In this context input-/synapse-specific effects (*CB* calbindin; *PV* parvalbumin) and TMS effects on non-neuronal cell types, i.e., glial (astrocytes, oligodendrocytes, microglia), endothelial, and immune cells, must be considered as well. It has become clear that rTMS can change structural, functional, and molecular properties of neurons, which may depend on the simultaneous induction of both anterograde and backward propagating action potentials. Neuromodulation is expected to play a fundamental role in this context. However, the precise role of rTMS in promoting, blocking, or shifting the balance between distinct forms of plasticity remains to be determined. (**b**, **c**) Illustration of potential direct or indirect molecular targets of rTMS. (**b**) Experimental evidence suggests that rTMS-induced plasticity requires the activation of voltage-gated sodium channels (VGSCs), N-methyl-D-aspartate receptors (NMDARs), and L-type voltage-gated calcium channels (L-VGCCs) during stimulation. The induced changes in excitatory synaptic strength (long-term potentiation/depression, respectively; LTP/LTD) are linked to the molecular reorganization of dendritic spines and postsynaptic densities (PSD95), including the phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and changes in synaptic AMPAR content. An involvement of presynaptic mechanisms (VGlut1; vesicular glutamate transporter 1), metabotropic neurotransmission (mGluR; metabotropic glutamate receptors and its anchoring protein Homer 1a), and remodeling of the cytoskeleton have been reported in this context as well. (**c**) While the precise intracellular signaling pathways of rTMS-induced plasticity remain not well understood, brain-derived neurotrophic factor (BDNF) and cyclic adenosine monophosphate (cAMP)-dependent signaling pathways have been identified to play an important role. These and other pathways could be involved in rTMS-mediated changes in gene expression profiles and proteostasis

Table 2.1 Major forms of neural plasticity

Form of plasticity	Short summary/definition
Hebbian plasticity	Named after Donald Hebb (1904–1985), this form of associative plasticity, in which simultaneous or rapid sequential activation of two synaptically connected neurons leads to a change in the strength of synapses between them (James 1890), describes structural, functional, and molecular adaptations of neurons that are considered to underlie experience-dependent network changes, as seen in the context of learning and memory. A classic experimental approach to study this form of plasticity is electrical induction of long-term potentiation (LTP; Bliss and Lomo 1973). The discovery of spike timing-dependent plasticity (Markram et al. 1997; Bi and Poo 1998; Song et al. 2000) supported the temporal causality proposed by Hebb (i.e., "cell A firing cell B," Hebb 1949) to play an important role in promoting specific changes in network connectivity.
Homeostatic plasticity	Describes compensatory mechanisms, which promote stability of neural networks despite ongoing (experience-dependent) changes (Davis 2006; Marder and Goaillard 2006; Turrigiano 2008; Pozo and Goda 2010). Involves the modification of intrinsic, synaptic, and structural properties of neurons that aim at keeping functionality in neural networks within a proper dynamic range. If, for example, network activity increases, neurons will respond after a while with a compensatory reduction in excitatory synaptic strength (or an increase in inhibitory synaptic strength).
Metaplasticity	Subsumes mechanisms, which regulate the duration, direction, and extent of associative plasticity, without directly affecting neural excitability, transmission, and connectivity (Abraham and Bear 1996). This form of plasticity controls the ability of neural networks to express plasticity ("plasticity of plasticity").

stimulation initiates action potentials preferentially in low-threshold interneurons (Pashut et al. 2014), resulting in a suppression of the stimulated cortex for about 200 ms after stimulation (Kozyrev et al. 2014). Conversely, high-frequency repetitive magnetic stimulation (10 Hz; or single-pulse stimulation with higher intensity) seems to shift the balance between excitation and inhibition toward excitation (Kozyrev et al. 2014). Additional work is now required to better understand how structural and functional properties of individual neurons and specific network architectures influence the outcome of single-pulse and repetitive magnetic stimulation.

In this context, recent work has also indicate that rMS may assert its effects by simultaneously depolarizing pre- and postsynaptic neuronal compartments, i.e., through the induction of both anterograde and backward propagating action potentials (Lenz et al. 2015). Hence, simultaneous recordings of distinct cells or dual recordings from individual neurons, e.g., somato-dendritic recordings, are expected to provide new important insights into the effects of rTMS during stimulation at the single-cell level. The impact of rTMS on non-neuronal cell types in the brain (e.g., astrocytes, microglia, oligodendrocytes, endothelial cells, immune cells) remains to be determined (Fig. 2.1a).

2.3 Repetitive Magnetic Stimulation Induces Plasticity of Excitatory Synapses

Early reports in human subjects have demonstrated that rTMS can increase or decrease cortical excitability beyond the stimulation period (Chen et al. 1997; Ziemann et al. 2008). It was noted that stimulus intensity, frequency, and the state of the stimulated network influence the duration, direction, and extent of rTMS-induced changes in cortical activity (for details, see Chap. 1). These after-effects of rTMS have been assumed to represent changes in synaptic efficacy and were therefore termed "long-term potentiation and depression (LTP/LTD)-like" phenomena, respectively. Hence, it was proposed that rTMS could assert its beneficial effects in the context of neurological and psychiatric disease by interfering with Hebbian forms of plasticity, e.g., LTP/LTD, which is considered to underlie learning and memory processes. Accordingly, animal studies have been employed to assess the effects of rTMS on synaptic plasticity. Initial experimental evidence for rTMS-induced synaptic activity was derived from immunostainings for immediate early gene (IEG)-encoded proteins, such as c-fos and zif-268 (e.g., Barth 2007; Loebrich and Nedivi 2009; Okuno 2011; Smeyne et al. 1992), which are recruited in the early stage of synaptic plasticity. Although robust experimental evidence has been provided that rTMS recruits IEG-encoded proteins, increased levels of c-fos and zif-268 were observed independent of stimulation frequency and pattern (Aydin-Abidin et al. 2008; Hausmann et al. 2000, 2001; Hoppenrath and Funke 2013; Volz et al. 2013). Yet, it was noted that rTMS may activate distinct brain regions and specific neurons within stimulated networks (Ji et al. 1998). Likewise, immunostainings for presynaptic (Vlachos et al. 2012; Volz et al. 2013) and postsynaptic markers (Gersner et al. 2011; Lenz et al. 2015; Ma et al. 2013; Vlachos et al. 2012; Fig. 2.1b) provided evidence that synaptic changes may underlie rMS-induced plasticity. More recent work in organotypic slice cultures was able to provide direct experimental evidence at the single-cell level that rMS is capable of inducing long-lasting functional and structural synaptic plasticity, that is an N-methyl-D-aspartate receptor (NMDAR)-dependent, Ca^{2+}-mediated enlargement of dendritic spines and strengthening of excitatory synapses (Vlachos et al. 2012; Lenz et al. 2015). These studies are in line with earlier in vivo and in vitro work (e.g., Levkovitz et al. 1999; Tokay et al. 2009) supporting the notion that rTMS of the human cortex may induce Hebbian-type synaptic plasticity, i.e., LTP of excitatory synapses.

Although rMS has been shown (1) to require the activation of voltage-gated sodium channels (VGSC); (2) to be Ca^{2+}-dependent, i.e., requiring the activation of both NMDAR and L-type voltage-gated calcium channels (L-VGCC) (Vlachos et al. 2012; Lenz et al. 2015); (3) to recruit intracellular signals such as cAMP-CREB (Hellmann et al. 2012); and (4) to depend on BDNF-TrkB signaling (Fig. 2.1c; Wang et al. 2011; Ma et al. 2013), the precise downstream signaling pathways leading to LTP of excitatory synapses following rTMS, such as phosphorylation and/or accumulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) at excitatory postsynapses (Gersner et al. 2011; Vlachos et al. 2012; Lenz et al. 2015), warrant further investigation

(Fig. 2.1b, c). Future studies employing (opto-)genetic, pharmacologic, computational, and other experimental approaches will help in delineating similarities and differences between LTP mechanisms recruited by electromagnetic vs. local electric stimulation and may help in defining specific stimulation parameters for the effective induction of structural, functional, and molecular plasticity of distinct synapses in defined cortical networks by rTMS.

2.4 Repetitive Magnetic Stimulation Affects Inhibition and Neuronal Excitability

In addition to its effects on excitatory synapses, rTMS is expected to also modulate inhibitory neurotransmission. A variety of activity markers and calcium-binding proteins of inhibitory interneurons have been assessed in this context (e.g., Labedi et al. 2014; Mix et al. 2014, 2015; Trippe et al. 2009). For instance, it has been shown that intermittent theta-burst stimulation reduces parvalbumin (PV)-expression in fast-spiking interneurons, while continuous theta-burst stimulation and 1 Hz rTMS predominantly affect calbindin (CB)-expression in cortical areas (Benali et al. 2011; Trippe et al. 2009; Volz et al. 2013). As PV-expressing interneurons primarily control pyramidal cell output, i.e., somatic inhibition, whereas CB-expressing interneurons are considered to regulate pyramidal cell input, i.e., dendritic inhibition (c.f., Fig. 2.1a), these findings imply that distinct rTMS protocols may affect specific aspects of inhibition and hence network activity and function (Funke and Benali 2011; see also Mix et al. 2014, 2015). In line with this notion, TMS-EEG experiments in humans demonstrate that GABAergic inhibitory neurotransmission has a major impact on cortical excitability and connectivity (Premoli et al. 2014). However, direct experimental evidence for the effects of rTMS on inhibition is still missing, since to date no studies are available assessing rTMS-induced structural and functional changes of GABAergic synapses on principle neurons (or excitatory synapses on inhibitory interneurons). Similarly, a comprehensive analysis of rTMS effects on passive and active intrinsic cellular properties, e.g., voltage-gated sodium, potassium, chloride, and calcium currents, is required to better understand the effects of rTMS on excitation and inhibition (E/I) balance in neural circuits and their relevance for plasticity.

2.5 The Role of rTMS-induced Structural Plasticity in Modulating Network Connectivity

Structural changes, such as axonal sprouting and pruning, remodeling of the dendritic tree, dendritic spine turnover, and the formation or loss of excitatory and inhibitory synapses, continuously modify connectivity in the CNS. Since structural plasticity is known to depend on neural activity, it is conceivable that rTMS could assert long-lasting effects on neural networks by inducing the structural remodeling of neural networks. However, so far only one published study exists, which has employed in vitro live-cell microscopy to assess the dynamics of rMS-induced structural plasticity (Vlachos et al. 2012). In this

study an increase in the volume of dendritic spines was reported to occur predominantly in small spines, while no effects on spine numbers were observed after high-frequency (10Hz) rMS (Vlachos et al. 2012). These findings are consistent with recent data on spine densities obtained from fixed tissue in vivo (Sykes et al. 2013). Since synapses on small spines are known to constitute weak synapses with low numbers or even no AMPARs (so-called silent synapses containing mainly NMDARs; e.g., Hanse et al. 2013; Kerchner and Nicoll 2008), it is possible that rTMS could modulate network connectivity by recruiting these weak or silent synapses without the need of additional spino- or synaptogenesis. It is tempting to speculate that a simultaneous depolarization of pre- and postsynaptic compartments, i.e., rTMS-induced anterograde (aAP) and backward propagating action potentials (bAP), may recruit silent synapses by increasing the probability of presynaptically released glutamate to activate postsynaptic NMDARs in the absence of AMPARs (see "bAP-aAP theory" in Lenz et al. 2015). Apparently, more work is required to clarify the contribution of "synaptic unsilencing" in rTMS-induced plasticity (see also Rodger et al. 2012) and to determine the effect of single vs. repeated rTMS sessions on structural properties (i.e., axons, dendrites, spines, synapses) of individual neurons, and other cells in the CNS.

2.6 Repetitive Magnetic Stimulation Modulates Gene Expression Profiles

Experimental evidence indicates that rTMS can modify gene expression profiles relevant for neural plasticity (Müller et al. 2000; Stock et al. 2012; Okada et al. 2002). However, it remains to be shown how rTMS-induced changes in gene expression affect proteostasis (i.e., the balance between biogenesis, folding, trafficking, and degradation of specific proteins; for review on proteostasis, see, e.g., Mardones et al. 2014), in distinct neural compartments, and how the observed effects influence the ability of neurons to express plasticity (Fig. 2.1). Neuroprotective, e.g., expression of neurotrophic factors such as BDNF (e.g., Gersner et al. 2011), but also toxic effects (Fang et al. 2010; Fujiki and Steward 1997; Okada et al. 2002) of rTMS must be considered in this context as well.

2.7 The Role of Neuromodulators in rTMS-induced Plasticity

Neuromodulation is another relevant aspect to consider in the context of rTMS-induced plasticity (e.g., Vahabzadeh-Hagh et al. 2012). It is plausible that dopamine, serotonin, acetylcholine, adrenaline, and other neuromodulators may affect the outcome of rTMS. In turn, it is possible that rTMS may act on these neuromodulatory systems to influence plastic properties of neuronal networks beyond the stimulation period.

Indeed, human studies disclose that rTMS-induced LTP- and LTD-like plasticity in the primary motor cortex depends on neuromodulation (Korchounov and Ziemann 2011; Thirugnanasambandam et al. 2011; for review, see Ziemann et al. 2015). Similarly, alterations in rTMS-induced motor cortex plasticity were reported in a rat

model of Parkinson's disease, which correlated with behavioral deficits and neuronal cell loss in the substantia nigra (Hsieh et al. 2015), therefore pointing toward a role of dopamine in rTMS-induced plasticity. On the other hand, several animal studies (in vitro and in vivo) indicate stimulus- and site-specific rTMS effects on the expression of neuromodulators, their receptors, and transporters (e.g., Ben-Shachar et al. 1999; Erhardt et al. 2004; Ikeda et al. 2005; Keck et al. 2002; Kole et al. 1999; Zangen and Hyodo 2002). A better understanding of the role of neuromodulation in rTMS-induced plasticity may thus support the development of novel means in early diagnosis, prognosis, and therapy of brain diseases, e.g., by combining pharmacological neuromodulation with specific rTMS protocols.

2.8 Translation into Clinics and Future Directions

As outlined in this book, numerous clinical studies have investigated and confirmed the therapeutic potential of rTMS in various brain diseases (see also Lefaucheur et al. 2014). However, our knowledge of the cellular and molecular mechanisms underlying rTMS-based therapies remains limited. Considering experimental advances in this field of research during the past decade, a biologically driven attempt to improve the use of rTMS in clinical practice has started to emerge, which may also help to better understand the considerable degree of inter- and intraindividual variability of rTMS effects seen in human subjects (see Chap. 1). However, this attempt can only go hand in hand with a better understanding of the role of neural plasticity under pathological conditions (Maggio and Vlachos 2014). For example, it remains unclear through the induction/modulation of which form(s) of plasticity (i.e., Hebbian plasticity, homeostatic plasticity, metaplasticity) rTMS could assert its beneficial effects in the course of a neurological or psychiatric disease (Müller-Dahlhaus and Vlachos 2013). In this context, rTMS effects on non-neuronal cell types need to be considered as well. To successfully transfer knowledge on the cellular and molecular mechanisms of repetitive magnetic stimulation into more effective therapies in neurological and psychiatric patients, it will be also important to study rTMS effects in animal models of brain diseases (e.g., by using genetic mouse and rat models of depression; Barkus 2013). We are confident that these studies will help building evidence-based frameworks for the clinical use of rTMS in the future (for review, see Nitsche et al. 2012).

Eventually the knowledge gained from animal studies may be translated into clinical practice (1) by optimizing the efficacy and specificity to detect, induce, and/or modulate certain forms of neural plasticity with rTMS; (2) by using knowledge about the state dependency of rTMS-induced plasticity (e.g., understanding the role of genetic polymorphisms and gene/protein expression profiles, neuromodulators, homeostatic plasticity, and metaplasticity); or (3) by combining rTMS with other therapeutic interventions (e.g., pharmacological neuromodulation) in order to support specific rTMS effects. Together with increasing knowledge on the role of large-scale neural networks for task-specific computations (see next chapter) and a better knowledge on plasticity under pathological conditions, these lines of research could pave the way toward more effective and personalized rTMS treatments of patients with neurological and psychiatric diseases.

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Basic Principles of rTMS in Motor Recovery After Stroke

3

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) can be used to promote recovery of motor function after stroke. We are only beginning to understand the neural underpinnings of stimulation after-effects on motor function. In this chapter, we summarize scientific evidence that motivates the rationale behind the two major rTMS approaches used in the rehabilitation of stroke patients. Finally, we present promising novel developments and future prospects that might help to pave the way to clinical applications of rTMS in stroke.

3.1 Introduction

An ischemic brain lesion induces a cascade of various cellular processes that aim at limiting tissue loss in hypo-perfused but still vital tissue (i.e., the *penumbra*). Concurrently, structural and functional changes in both perilesional and remote regions are engaged in compensating the stroke-induced loss of neural tissue, referred to as *neural plasticity* (for a review, see Nudo 2013). Noninvasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) enables the induction of neural plasticity which is thought to derive from a modulation of synaptic transmission in terms of long-term potentiation (LTP)-like or long-term depression (LTD)-like processes (see Chap. 1 for further details). rTMS therefore offers the opportunity to interact with cortical reorganization following stroke (Hallett 2000). In the past two decades, a number of studies have already

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evaluated the potential of rTMS in a neurorehabilitative setting (see Chap. 4 for a summary on clinical data). From a mechanistic point of view, two stimulation strategies have been proposed to support post-stroke motor recovery: rTMS may either be used to (i) enhance cortical excitability of the ipsilesional hemisphere or (ii) decrease cortical excitability of the contralesional hemisphere. In the following chapter we will summarize data that motivates the rationales for the utilization of rTMS as a promising tool to support motor rehabilitation following stroke.

3.2 Effects on Ipsilesional Motor Cortical Excitability

Two noninvasive approaches have been frequently used to assess cerebral reorganization following stroke: (i) transcranial magnetic stimulation (TMS) and (ii) neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). TMS can be used to investigate electrophysiological properties of the motor system. For example, stimulation of the primary motor cortex (M1) induces neural activity, which descends through the corticospinal tract (CST) and ultimately triggers contraction of peripheral muscle fibers, resulting in motor evoked potentials (MEPs), which are recorded via *electromyography* (see Chap. 1 for further details). Following stroke, MEPs evoked from the ipsilesional hemisphere are typically reduced in amplitude or even absent (Abbruzzese et al. 1991; Catano et al. 1996; Delvaux et al. 2003). Of note, the degree of reduction in excitability reduction has been shown to predict the potential of functional recovery, with stronger decreases in excitability featured by patients with less favorable outcome (Hendricks et al. 2002). Especially patients with stronger damage to the CST feature stronger reduction in motor cortical excitability (Volz et al. 2015). The presence or absence of an MEP upon stimulation of the affected hemisphere constitutes a critical criterion to determine whether patients with strong initial motor impairment will recover or not (Stinear et al. 2007, 2012). Likewise, functional recovery over time is associated with increases in ipsilesional MEP amplitudes (Cicinelli et al. 1997; Traversa et al. 1997, 1998). Therefore, the close relationship between MEPs evoked from the ipsilesional hemisphere and motor function has stimulated the idea that increasing MEP amplitudes via the application of excitatory rTMS may counterbalance the initial reduction of MEP amplitudes in stroke patients and thereby ameliorate hand motor function (Kim et al. 2006; Talelli et al. 2007). From a mechanistic perspective, the question arises whether this beneficial rTMS effect may be due to the modulation of stroke-induced intracortical processes that are involved in cortical reorganization.

Double-pulse TMS protocols allow the investigation of intracortical excitability and its neural underpinnings. The principle behind double-pulse TMS is founded in the observation that applying two consecutive pulses over M1 results in the modulation of the MEP elicited by the second stimulus. The response to the

second, i.e., *test*, stimulus is affected by the first, i.e., *conditioning*, stimulus even though the latter is typically applied at subthreshold intensity, hence does not elicit an MEP itself (Kujirai et al. 1993). Using interstimulus intervals of 1–6 ms typically results in a reduction of the *test* stimulus' amplitude, which is referred to as *short-interval intracortical inhibition* (SICI). In contrast, longer interstimulus intervals (>7 ms) cause an increase in the MEP amplitude termed intracortical facilitation (ICF). Applying two suprathreshold pulses at longer interstimulus intervals (i.e., 100–200 ms) also results in inhibition of the activity induced by the *test* stimulus (*long-interval intracortical inhibition*—LICI) (Valls-Sole et al. 1992). Pharmacological studies suggest these intracortical TMS effects to derive from the stimulation of different interneuron populations and to depend on activity levels of inhibitory GABAergic interneurons or even subclasses of GABA-receptors (for a review see Ziemann 2011). Following stroke, decreases of SICI and LICI were reported, suggesting a reduction in GABAergic inhibition within the ipsilesional motor network (Liepert et al. 2000; Manganotti et al. 2002; Cicinelli et al. 2003). Liuzzi and colleagues reported stronger disinhibition of SICI in the acute phase post-stroke to predict motor recovery 1 year after stroke, independent of the initial deficit (Liuzzi et al. 2014), possibly indicating that reduced intracortical inhibition early after stroke may contribute to successful motor recovery. From a pathophysiological perspective, a reduction in intracortical inhibition might reflect cortical reorganization by reduction of inhibitory GABAergic activity. Support for this hypothesis stems from studies in animal models which reported an initial upregulation of $GABA_A$-activity within perilesional tissue (possibly reducing excitotoxicity and cell death) (Clarkson et al. 2010), followed by a downregulation of $GABA_A$ergic signaling (Redecker et al. 2002). Interestingly, rTMS seems to interact with GABAergic activity. For example, animal studies showed that rTMS leads to short-lasting increases in the activation of GABAergic synapses which are paralleled by a long-lasting reduction of GABAergic interneuron activity (Funke and Benali 2011; Volz et al. 2013). Evidence obtained from studies with human subjects assessing GABA concentrations within the motor cortex via magnetic resonance spectroscopy (MRS) supports the idea that the induction of neural plasticity via rTMS or motor learning might in part derive from the modulation of GABAergic cortical inhibition (for a review see Bachtiar and Stagg 2014).

In summary, the investigation of altered electrophysiological properties of the affected hemisphere post-stroke suggests at least two concurrent mechanisms to be informative of the individual potential for functional recovery after stroke: (i) altered MEP amplitudes and thresholds reflecting functional CST integrity and (ii) paired-pulse TMS suggesting motor cortical disinhibition within the affected hemisphere. Swayne and colleagues directly compared the predictive potential of both changes in MEPs and SICI in acute stroke patients (Swayne et al. 2008). Here, the initial reduction in cortical excitability (MEPs induced at different intensities, *recruitment curves*) of the ipsilesional M1 was strongly associated with both initial motor

impairment and early motor recovery (4 weeks post-stroke). However, motor impairment at later stages (6 months) was more accurately predicted by changes in intracortical excitability. Hence, both properties might represent distinct yet complementary factors influencing individual recovery from stroke. One explanation could be that motor impairment primarily depends on damage to corticospinal output, in the acute stage, while at later stages—as a consequence of perilesional reorganization—motor performance is also based on the recruitment of alternate networks that allow to maximize the efficiency of remaining corticospinal pathways (Swayne et al. 2008).

3.3 System Level Mechanisms: Model of Interhemispheric Competition

While TMS is useful to study stroke-induced changes in M1 properties, more general effects of stroke on motor system activity can be assessed by (functional) neuroimaging. In stroke patients, functional neuroimaging studies frequently revealed higher levels of neural activation during movements of the paretic limb compared to healthy subjects (Chollet et al. 1991; Weiller et al. 1992; Ward et al. 2003; Gerloff et al. 2006; Grefkes et al. 2008). Of note, this "over-activation" is not limited to the ipsilesional hemisphere but also extends into the contralesional "healthy" hemisphere. The latter finding has stimulated the discussion about the functional role of the contralesional hemisphere for post-stroke recovery. In healthy subjects, simple unilateral motor tasks such as wrist-flexions or fist-closures typically cause a strongly lateralized pattern of activation with activity changes primarily occurring in motor areas within the hemisphere contralateral to the moving hand. However, increasing movement complexity, e.g., during sequential finger movements, leads to the additional recruitment of ipsilateral motor regions resulting in a more bilateral motor activation (Verstynen et al. 2005; Hummel et al. 2003). Hence, it seems possible that after stroke, simple movements of the paretic limb may be processed like complex movements in healthy subjects, with recruitment of bilateral motor areas possibly supporting movement execution (Di Pino et al. 2014). Such a *vicariation* model, suggesting a functional compensation of lesioned areas by contralesional regions, is supported by studies using TMS over contralesional motor areas during motor tasks performed with the paretic hand. Lotze and colleagues showed that transiently disrupting activity within the contralesional hemisphere may deteriorate motor function of the paretic hand (Lotze et al. 2006), thus suggesting contralesional neural activity to functionally compensate for the structural damage of the ipsilesional hemisphere. Further support for this hypothesis derives from neuroimaging data. In subacute stroke patients, Rehme and colleagues reported the amount of "over-activation" of contralesional motor areas to correlate with subsequent functional recovery (Rehme et al. 2011). In line with this finding, the pharmacological inactivation of the contralesional hemisphere 3–4 weeks post-stroke was shown to further deteriorate motor function of the paretic forelimb in rats (Biernaskie et al. 2005). In macaques, Nishimura and

colleagues (2007) observed that after CST lesions (introduced on the cervical level) motor recovery after 4 weeks was associated with increased neural activity in bilateral M1, whereas recovery at later stages (after 3 months) primarily correlated with activity of M1 contralateral to the affected hand. Accordingly, pharmacological inactivation of the M1 ipsilateral to the affected hand worsened its motor function at the early but not the chronic stage (Nishimura et al. 2007). These findings underline the time-dependent role of contralesional motor activity, with a supportive influence early after stroke that declines with time (Grefkes and Ward 2014). This line of arguments may also help to explain why neuroimaging studies conclusively found persisting "over-activation" of the contralesional hemisphere at chronic stages post-stroke to mostly occur in patients featuring a less favorable outcome (Ward et al. 2003; Rehme et al. 2011). However, this leads to the question which functional role the "over-activation" of the contralesional hemisphere might play from a systems-level perspective, e.g., how contralesional activity influences the ipsilesional hemisphere.

Two independent methodological approaches have frequently been used to non-invasively investigate interhemispheric interactions of motor areas in human subjects: (i) double-pulse TMS protocols and (ii) connectivity analyses based on neuroimaging data. For example, Ferbert and colleagues introduced a TMS protocol to assess interhemispheric inhibition (IHI) between bilateral M1 (Ferbert et al. 1992). A TMS pulse (*test* pulse) is applied to M1 of one hemisphere, and the resulting MEP is recorded from a muscle of the contralateral hand. Then a *conditioning* pulse is applied to M1 of the respective other hemisphere preceding the test pulse by several (e.g., 10) milliseconds. Of note, the conditioning stimulus is applied at subthreshold intensity, i.e., does not elicit an MEP itself. As a consequence of the *conditioning* pulse, the amplitude of the MEP elicited by the *test* pulse is reduced compared to a non-conditioned test stimulus (reduction up to 90 % or more). This phenomenon is referred to as interhemispheric inhibition (IHI) and is thought to derive from the activation of transcallosal pathways (Ferbert et al. 1992). During the preparation and execution of unilateral hand movements, IHI exerted by M1 ipsilateral to the moving hand targeting M1 contralateral to the moving hand is reduced (disinhibited) to "release" the planned action (Duque et al. 2007; Hinder 2012; Hinder et al. 2010). However, in chronic stroke patients, Murase and colleagues observed a lack of movement-related disinhibition from the contralesional M1 onto the ipsilesional M1 for movements of the paretic hand (Murase et al. 2004). Thus, the contralesional M1 continued to inhibit the ipsilesional M1 in stroke patients with hand deficits. Of note, reduced modulation of IHI correlated with the level of motor impairment with patients suffering from severe deficits featuring weakest reduction of IHI. These data suggest that persisting inhibition exerted by contralesional M1 over ipsilesional M1 might further reduce motor skills of the stroke-affected hand beyond the dysfunction resulting from the structural damage. Such functional disturbances in the reorganized brain have been termed *maladaptive* as they might contribute to impaired motor function, a hypothesis often referred to as *interhemispheric competition model* (Fig. 3.1) (Nowak et al. 2009; Di Pino et al. 2014).

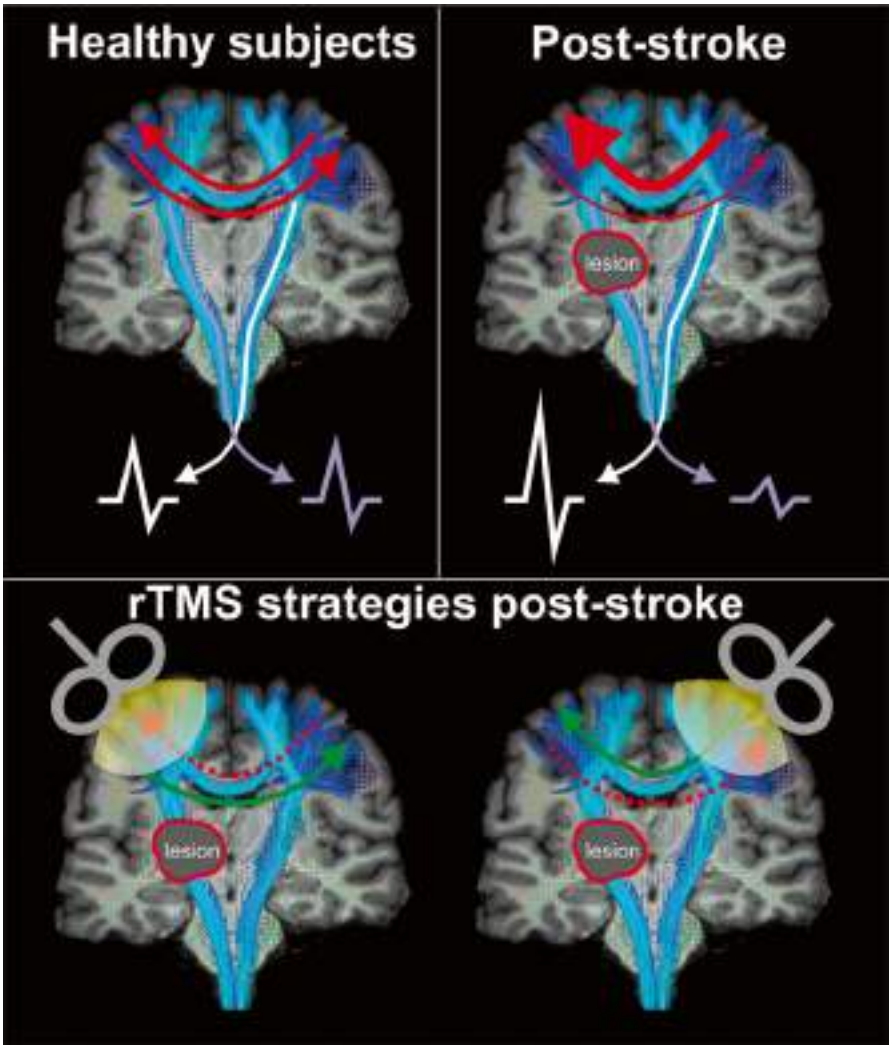

Fig. 3.1 Model of interhemispheric competition: In the healthy brain, interhemispheric inhibition (*red arrows*) is balanced between both M1 at rest, while unilateral movement is associated with a shift toward stronger inhibition of M1 ipsilateral to the moving hand. After stroke, interhemispheric inhibition targeting the contralesional hemisphere decreases while inhibition exerted over ipsilesional M1 is enhanced. This imbalance is also evident in the amplitudes of MEPs evoked from both hemispheres, with increased output observed from contralesional M1 (*white MEP*) and diminished MEPs elicited from ipsilesional M1 (*purple MEP*). According to this theoretical framework, applying excitatory rTMS over the ipsilesional M1 (*left side*) will increase cortical excitability and inhibition of the contralesional M1 (*green arrow*), thereby counterbalancing excessive inhibition exerted by contralesional M1 (*dashed red arrow*). Alternatively, interhemispheric imbalance can be adjusted by applying inhibitory rTMS applied to contralesional M1 (*right side*), which diminishes excessive inhibition of ipsilesional M1 (*green arrow*)

This hypothesis is strongly supported by neuroimaging data. As described above, numerous neuroimaging studies have reported altered movement-associated neural activity after stroke. However, knowing where activity is altered after stroke does not allow to draw conclusions about how a particular region interacts with other parts of the brain. In the last two decades, several approaches have been developed to assess from time series of imaging data how different brain regions interact (Eickhoff and Grefkes 2011). In this context, two different types of connectivity concepts can be distinguished: (i) "functional connectivity" refers to correlations (or coherence) between the time-courses of different regions. Here, higher correlation parameters are interpreted as stronger functional connectivity between the regions of interest. However, functional connectivity cannot distinguish how interactions are mediated and whether one region drives activity of the respective other region. To this end, model-based approaches such as dynamic causal modeling (DCM) allow to estimate "effective connectivity," i.e., the causal influences that one region exerts over another (Friston et al. 2003; Stephan et al. 2010). Grefkes and colleagues used DCM to evaluate cortical connectivity during simple unilateral hand movements in stroke patients with persisting motor deficits (Grefkes et al. 2008). In accordance to the TMS results of Murase and colleagues (2004), an inhibitory influence was exerted by contralesional M1 onto ipsilesional M1 during movements of the paretic hand, which was absent for movements of the unaffected hand or in healthy subjects. Moreover, the strength of this inhibition correlated with the degree of impairment across the cohort, with most severely impaired patients featuring strongest inhibitory influences targeting ipsilesional M1 (Grefkes et al. 2008). These findings corroborate a maladaptive role of the contralesional M1. As a consequence, suppressing the contralesional hemisphere might alleviate maladaptive influences exerted over the ipsilesional hemisphere, ultimately resulting in functional benefits for the paretic hand. Indeed, several studies have indicated that inhibitory rTMS applied to the contralesional M1 improves hand function in some patients (for further information see Chap. 4). A single application of inhibitory rTMS has been shown to also reduce neural over-activation of the contralesional hemisphere during movements of the paretic hand (Nowak et al. 2008). Hence, from a mechanistic perspective, reducing cortical excitability in the contralesional M1 transiently normalizes movement-related cortical activation. According to the interhemispheric competition model, reducing over-activation within the contralesional hemisphere will also reduce interhemispheric inhibition targeting the ipsilesional M1. Indeed, Grefkes and colleagues (2010) could show that inhibitory 1-Hz rTMS applied to contralesional M1 beneficially impacts on motor function of the affected hand and also reduces maladaptive interhemispheric inhibition targeting ipsilesional M1. Of note, the effects on motor behavior and connectivity significantly correlated, with stronger reduction in maladaptive inhibition observed in patients featuring strongest transient motor improvements after stimulation (Grefkes et al. 2010). Thus, rTMS-induced inhibition seems to promote motor function of the paretic hand through attenuating excessive interhemispheric inhibition onto ipsilesional M1.

The model of interhemispheric competition also supports the alternative rTMS-approach: enhancing motor activity within the ipsilesional hemisphere might strengthen IHI onto the contralesional hemisphere, which in turn could ultimately reduce pathological inhibition onto ipsilesional M1 (Grefkes and Fink 2012). One might argue that this hypothesis derived from the combination of electrophysiological data obtained via TMS and estimates of effective connectivity obtained via DCM from fMRI data seems far-fetched and that a beneficial impact of excitatory rTMS applied to the ipsilesional motor cortex rather stems from local effects within ipsilesional M1, such as induction of cortical plasticity or reduction of intracortical inhibition. However, we recently observed a strong relationship between reduced cortical excitability of the ipsilesional hemisphere (assessed via TMS) and reduced inhibition from ipsilesional M1 onto contralesional M1 assessed via DCM, which were both most reduced in chronic stroke patients suffering from severest motor deficits (Volz et al. 2015). Given these observations, enhancing cortical excitability within the ipsilesional hemisphere via rTMS could improve the interhemispheric balance of inhibition, ultimately alleviating maladaptive inhibition targeting the ipsilesional hemisphere. Support for this hypothesis stems from a study published by Ameli and colleagues, who observed that a single application of excitatory 10-Hz rTMS to ipsilesional M1 transiently increases motor function of the paretic hand and also reduces over-activation of the contralesional M1 (Ameli et al. 2009). Since the contralesional hemisphere was not directly stimulated, stimulation-induced changes in the ipsilesional hemisphere must have caused the observed reduction in contralesional activity, possibly via transcallosal connections on a cortical level. Of note, normalization of neural activation and motor function could only be achieved in patients suffering from subcortical stroke, whereas patients with cortical damage showed no reduction of contralesional activity (Ameli et al. 2009). This dependence on intact cortical tissue further corroborates that a beneficial effect of ipsilesional rTMS might, at least in part, derive from the modulation of cortical interactions within and across hemispheres.

In summary, the model of interhemispheric competition constitutes two hypotheses regarding systems-level mechanisms underlying beneficial effects of both excitatory rTMS applied to ipsilesional M1 and inhibitory rTMS applied to contralesional M1. Both approaches have been shown to transiently promote motor function, at least in certain patient populations. However, it must be kept in mind that the model of interhemispheric competition certainly oversimplifies the complex interactions between motor regions underlying the preparation and execution of voluntary movements and fails to include other important factors influencing motor recovery, e.g., lesion size and location. Furthermore, it contradicts observations that for some patients contralesional areas hold a compensatory role for motor recovery, especially early after stroke. Therefore, Di Pino and colleagues recently suggested combining both models (the *vicariation model* and *interhemispheric competition model*) by adding information on the individual extent of the structural damage caused by ischemia: size and location of a stroke lesion might determine whether motor areas of the non-lesional hemisphere rather hold a compensatory function or represent maladaptive plasticity (for further details see Di Pino et al. 2014).

3.4 When to Stimulate?

Most studies assessed rTMS effects on motor recovery in chronic stroke patients (Bates and Rodger 2014). However, strongest improvements in motor function occur in the first days to weeks after stroke, and motor deficits reach a stable plateau after 3–6 months post-stroke (Langhorne et al. 2011). Animal studies showed that cellular processes associated with neural plasticity are most pronounced in the first weeks after stroke, suggesting a critical time window for functional reorganization (for a review see Hermann and Chopp 2012). As discussed above, early increases in neural activity in contralesional areas correlate with better recovery during this period, implying a supportive role for hand motor function. Hence, applying inhibitory rTMS to the contralesional hemisphere seems to be more suited at later stages, i.e., when pathological interhemispheric inhibition has evolved. Given that the early post-stroke period is characterized by a loss of motor activity in the lesioned hemisphere, it seems reasonable to support recovery of function by stimulating the ipsilesional hemisphere. Animal studies suggest that rTMS applied to ipsilesional M1 early after stroke may also affect penumbral tissue by attenuating apoptosis (i.e., programmed cell death) along the infarct rim (Yoon et al. 2011).

3.5 The Concept of Diaschisis

Another possible mechanisms potentially adding to early motor impairment lies in the concept of *diaschisis*. In this concept postulated by von Monakow (1914), an acute lesion to one part of the brain consecutively leads to a reduction of input into regions remote of but connected to the lesion. Accordingly, recovery of function is partly thought to reflect a reactivation of initially functionally deafferented brain regions, as indicated by restored connectivity between motor regions. Recently, several studies described a time-dependent change in interhemispheric functional motor connectivity after stroke in both humans and animal models: an early decrease is followed by re-increasing connectivity alongside early motor recovery (Carter et al. 2010; van Meer et al. 2010; Park et al. 2011). These time-dependent changes have repeatedly been discussed to possibly reflect diaschisis, with the re-increase in interhemispheric functional connectivity representing alleviation of diaschisis (for reviews see Carrera and Tononi 2014; Silasi and Murphy 2014). Nettekoven and colleagues could show that excitability-enhancing rTMS applied to M1 in healthy subjects increases functional motor network connectivity (Nettekoven et al. 2014). These findings give rise to the hypothesis that rTMS might also help to increase motor network connectivity in stroke patients and thereby alleviate diaschisis. Support for this hypothesis stems from a recent animal study, which reported repetitive stimulation of the ipsilesional M1 to induce the expression of neurotrophic factors in contralesional M1, strongly suggesting the stimulation to cause aftereffects not only locally but also in remote motor area (Cheng et al. 2014). Of note, the alleviation of diaschisis

represents a mechanism involved in recovery of motor function within the first weeks (Buma et al. 2013). Hence, rTMS may potentially support functional recovery via alleviation of diaschisis when applied within this period of time.

3.6 On the Way to Therapeutic Applications

Despite the remarkable body of literature suggesting a beneficial role of rTMS to promote motor functional recovery following stroke, rTMS has still not become a standard clinical procedure in stroke rehabilitation. The question arises what has thus far limited the TMS community to conduct randomized clinical trials in order to prove that rTMS can be used as a therapeutic tool (for further details see Bates and Rodger 2014). Several factors complicate the attempt to design an rTMS treatment protocol. First, which particular protocol should be used for either excitatory or inhibitory rTMS? Although this question is beyond the scope of this chapter, it should be noted that besides the modulatory potential of a given intervention, also stimulation duration, number of repetitions, and necessary stimulation intensities have to be considered. To this end, stimulation protocols that can be applied at low intensities and are of short duration, such as theta-burst stimulation (TBS) (Huang et al. 2005), represent promising candidates regarding clinical applications. In addition, recent findings imply that refining existing protocols like TBS might further enhance their neuromodulatory potential (Nettekoven et al. 2014), possibly resulting in larger effect sizes at the therapeutic level. Alternatively, different neuromodulatory protocols may be combined to increase stimulation effects. First, encouraging results are derived from a study by Sung and colleagues who found that sequential application of inhibitory rTMS to contralesional M1 followed by excitatory rTMS applied to ipsilesional M1 may induce stronger effects on motor function compared to either intervention applied alone (Sung et al. 2013). A further important factor lies in the combination with rehabilitative treatments and different forms of motor training. While several studies observed beneficial effects after combined rTMS and distinct forms of motor training such as physiotherapy (Khedr et al. 2005; Chang et al. 2010; Ackerley et al. 2010), Malcolm and colleagues (2007) observed no beneficial effect of combining excitability-enhancing rTMS and constraint-induced movement therapy (CIMT). Hence, these results suggest that certain combinations of rTMS and motor training may show stronger and more effective interactions affecting motor recovery than others, highlighting the need to identify suitable combinations of neuromodulatory interventions and training.

Recently, several studies in large cohorts of healthy subjects have shown that individual responses to rTMS approaches considerably differ across individuals (Hamada et al. 2013; Hinder et al. 2014). Several factors such as age, genetic factors, and electrophysiological and connectional properties of the motor network have been discussed to critically influence how TMS interacts with the brain (Cardenas-Morales et al. 2014; for a review see Ridding and Ziemann 2010). Of note, all these factors are associated with the interindividual variability in response to rTMS in healthy subjects. Considering the heterogeneity of stroke

lesions and their compensation, the amount of variance in individual susceptibility to rTMS in stroke patients possibly even exceeds the variability observed in healthy subjects. In fact, individual susceptibility might also partly account for inconsistent findings observed across different studies assessing rTMS effects in stroke patients (Grefkes and Fink 2012). Hence, the identification of surrogate markers that reliably predict the individual response to neuromodulatory approaches represents a highly important challenge, enabling the selection of suitable patients in a clinical context (Grefkes and Fink 2012). The utilization of *machine learning techniques* that allow inference on the level of single patients from multidimensional data (e.g., a combination of behavioral, electrophysiological, and neuroimaging information; for example, see Rehme et al. 2014) may help to identify whether a specific patient might be a suitable candidate for a given intervention.

Finally, continuously furthering our insights into neural mechanisms underlying both cortical reorganization occurring after stroke and its interaction with rTMS-induced activity by combining multimodal evidence from human research and animal models seems inevitable to appraise and extend the beneficial impact of rTMS on recovery of motor function following stroke.

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Clinical Applications of rTMS in Motor Rehabilitation After Stroke

4

Thomas Platz

Abstract

Both inhibitory and excitatory ipsilesional and contralesional non-invasive brain stimulation protocols (rTMS, TBS) have been applied during the acute, post-acute and chronic phases to improve motor recovery in stroke patients having upper and/or lower limb paresis. A best evidence synthesis based on RCTs and meta-analyses is presented that can be used for clinical decision making.

Taken together, there is a substantial database indicating that the above-mentioned rTMS applications are safe when the conventional safety recommendations are followed. The intervention that had best been investigated is contralesional M1 low-frequency (inhibitory) rTMS. The most focused meta-analysis reported to date documents an overall effect size of 0.55 on average for rTMS therapies in arm motor rehabilitation after stroke that can be considered moderate. Given the low risk profile and the demonstrated clinical benefits, there is reason to recommend and apply rTMS therapy in stroke patients with motor deficits, especially arm paresis.

4.1 Introduction

Stroke is the leading cause of long-term disability among adults. Even with appropriate acute care and neurorehabilitation, recovery of motor function after stroke is usually incomplete (Ward and Cohen 2004). More than 60 % of stroke survivors suffer from persistent neurological deficits with impaired motor function compromising their independence with activities of daily living activities (Feigin et al. 2003; Levin et al. 2009).

This chapter focuses on clinical applications of repetitive transcranial magnetic stimulation (rTMS) in motor rehabilitation after stroke and here again on active motor function as opposed to other symptoms associated with paresis such as

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spasticity. Indeed, non-invasive brain stimulation has been applied during the acute, postacute and chronic post-stroke phases to improve motor recovery in stroke patients having upper and/or lower limb paresis (Ayache et al. 2012).

The following 'inhibitory' (I) or 'excitatory' (E) types of rTMS have been used in arm motor rehabilitation (see also Chap. 3):

- Low-frequency (LF) rTMS (I) of the contralesional primary motor cortex (M1)
- Continuous theta-burst stimulation (cTBS) (I) of the contralesional M1
- High-frequency (HF) rTMS (E) of the ipsilesional M1
- Intermittent theta-burst stimulation (iTBS) (E) of the ipsilesional M1

Only evidence from RCTs and meta-analyses based on systematic reviews was used for this chapter because this type of evidence is least prone to bias and thus most useful for clinical decision making. The clinical research evidence has been searched and will be portrayed below. The chapter ends with a summary and best evidence synthesis that can be used for clinical decision making.

4.2 Clinical Evidence

4.2.1 Randomised Controlled Trials

4.2.1.1 Low-Frequency rTMS of the Contralesional Motor Cortex (LF-rTMS) (Fig. 4.1)

Liepert and colleagues (2007) showed as a 'proof of principle' in a cross-over laboratory experiment with a single session of M1 sham or 1 Hz rTMS (1,200 pulses, 90 % resting motor threshold [RMT] first dorsal interosseus muscle [FDI]) that contralesional M1 1 Hz rTMS can enhance finger dexterity in mildly affected patients with acute subcortical stroke. Comparable results had been shown by Mansur et al. (2005) for mildly affected stroke patients within 1 year after stroke. Contralesional M1 (but not premotor cortex [PMC]) 1 Hz rTMS (600 pulses, 100 % RMT) improved finger dexterity (as compared to sham) and reaction time measures, but not finger tapping. Takeuchi et al. (2005) demonstrated an effect of contralesional 1 Hz rTMS (1,500 pulses, 90 % RMT FDI) on cortical excitability and transcortical inhibition duration in subcortical chronic stroke patients. When rTMS was followed by training a pinching task (Takeuchi et al. 2008), acceleration and force (after training only) with a pinching task increased persistently (more than after sham stimulation), an effect that was still observed after 1 week suggesting the possibility of therapeutic effects by LF-rTMS.

Conforto and colleagues (2012) investigated both safety and preliminary efficacy of therapeutic LF-rTMS of the contralesional motor cortex as add-on therapy to outpatient customary rehabilitation for patients with mild to severe hand paresis, at an early stage (within 5–45 days) after unilateral ischaemic stroke. Thirty patients were randomly assigned to receive immediately before each 60-min rehabilitation treatment, either active (1 Hz, 1,500 pulses, 90 % RMT abductor pollicis brevis

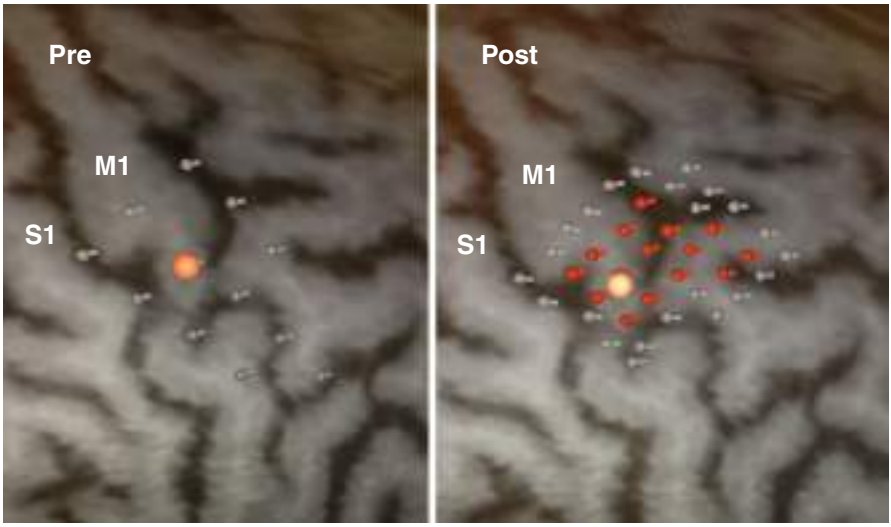

Fig. 4.1 Hand motor cortex mapping before and after a series of contralesional M1 LF 1 Hz rTMS. S1 denotes primary somatosensory cortex. In this case of a 75-year-old female patient, 5.5 weeks post right hemisphere subcortical stroke, mapping of the hand motor areas of the stroke hemisphere was performed before (*pre*) and after (*post*) a series of 1 Hz rTMS (110 % RMT, 900 stimuli, neuronavigated at the M1 hot spot of the abductor pollicis brevis muscle, APB in the non-lesioned hemisphere) for 18 sessions in 4 weeks. The *orange* target denotes the APB 'hot spot' based on the examination at 'post'. Mapping has been performed with 110 % of the RMT. *Grey* target denotes stimulation points with no MEPs (<50 μV); *red* targets indicate stimulation points where MEPs with an amplitude between 50 and 500 μV could be elicited (MEPs with amplitudes >500 μV could not be elicited in this case). Note that prior to rTMS no MEP could be evoked while there was an APB map with 15 active points (spaced 0.5 cm apart) after the series of contralesional M1 LF 1Hz rTMS. Clinically, the patient did not have active hand and only poor arm motor control prior to the rTMS series (Fugl-Meyer arm motor score, FM: 9; Action Research Arm test, ARAT: 0), while there was some active hand motor control afterwards (FM: 14; ARAT: 3). rTMS and mapping were performed with the Nexstim therapeutic system (Nexstim TM, Finland)

muscle [APB]) or sham rTMS, five times per week, during 2 weeks (ten treatment sessions). No serious intervention-related adverse events were observed; adverse events were similar between groups. Jebsen Taylor hand function test (JTHF) and pinch force improved only in the real rTMS group (inter-group difference were, however, n.s.), while Fugl-Meyer, arm motor score (FM arm) and modified Rankin Scale improved in both groups (inter-group difference again n.s.). With small effect sizes (0.16 at the end of treatment for real rTMS), the study was underpowered to corroborate an inter-group difference of the magnitude observed (JTHF). It must be concluded that 10 days of contralesional LF-rTMS did not generate large effects in subacute stroke patients with mild to severe hand paresis in this study.

Similarly, in a trial that compared 15 sessions of contralesional 1 Hz rTMS (1,800 pulses, 90 % RMT FDI) or sham therapy followed by 45 min of physiotherapy as Bobath treatment in subacute stroke patients, no benefit of rTMS could be documented (Wolf motor function test [WMFT], FM arm, NIH stroke scale

[NIHSS]) neither after the 3-week course of stimulation and training, nor at a 3 months follow-up (Seniów et al. 2012). The reasons for this failure remain uncertain. A considerable proportion of the study population had cortical involvement (26/40), yet the subpopulation analysis with subcortical infarcts showed the same picture as seen for the study population. Alternatively, it might be entertained that the type of training provided (Bobath therapy) might not have been optimal (compare Platz et al. 2005) and consequently training-induced changes to small for any modifying effect of rTMS. This interpretation would hold true if rTMS did not itself enhance motor recovery, but only as a modifier of training-induced changes.

When Theilig and colleagues investigated any modifying effects of contralesional 1 Hz rTMS priming on the effects of subsequent EMG-triggered electrostimulation in mainly subacute stroke patient with severe paresis (and varying somatosensory deficits), they did observe a substantial functional improvement of the affected arm (WMFT; appr. 20 % improvement) after 10 daily sessions of training, and yet there was again no additional benefit of the 1 Hz rTMS priming (900 pulses, 100 % RMT FDI, contralesional M1). Here there was a relevant recovery of function and still contralesional M1 LF-rTMS created no benefit. It seems therefore likely that there could be patient characteristics that cause the response or non-response that had not been known and controlled for. In the case of this study, the severe paresis, i.e. 20 out of 21 subjects had clinically a complete paralysis (MRC 0) of their wrist and finger extensors (and thus severe damage to the M1 cortex and/or corticospinal tract) could have been relevant, and 7 out of 11 had cortical involvement of their stroke. These aspects could have been factors preventing a substantial benefit by rTMS. It might be noted that 1 Hz rTMS did equally not have a detrimental effect here.

While multi-session contralesional 1 Hz rTMS has frequently been applied with 900–1,800 stimuli per session (15–20 min), shorter duration rTMS, e.g. 4 min (240 stimuli per session), combined with repetitive arm training could clinically be an interesting alternative option. Etoh and colleagues (2013) reported on a cross-over RCT with 18 ischaemic or haemorrhagic chronic stroke patients with mild to moderate arm paresis comparing 10 sessions of sham stimulation with contralesional 1 Hz rTMS (240 stimuli), each followed by 40 min of repetitive facilitating arm exercises and documented (small) superior effects after 1 Hz rTMS with the Action Research Arm test (ARAT); differences in gain for the Fugl-Meyer arm section or a timed measure of dexterity (STEF) were, however, not statistically significant. Accordingly, for this population a short-duration contralesional 1 Hz rTMS could enhance the training effect, at least to a limited degree.

Effects of rTMS and whether the location of ischaemic stroke including cortical versus non-cortical involvement affected responses to rTMS combined with training were investigated by Emara and colleagues (2009, 2010). Sixty subacute or chronic ischaemic stroke patients were randomised to receive short-duration 5 Hz rTMS to the ipsilesional M1 (750 pulses/session, 10 sessions), 1 Hz rTMS to the contralesional M1 (150 pulses/session, 10 sessions), or sham stimulation. While patients with subcortical damage improved (Activity Index) after contralesional 1 Hz rTMS, patients with cortical involvement did not. Patients receiving 5 Hz

ipsilesional rTMS improved with or without cortical involvement (between baseline and post rTMS as well as 2 weeks later). While this study used a relatively low dose of rTMS, it hints towards a modifying effect of cortical involvement when contralesional M1 1Hz rTMS is used.

To address the question whether it matters whether rTMS was applied before or after an arm training, Avenanti and colleagues (2012) randomly assigned 30 mildly paretic chronic stroke patients (stroke sparing M1) in 4 different groups, where stimulation was either real or sham and was administered either immediately before (rTMS-PT) or after PT (PT-rTMS). Patients received 10 daily sessions of 1 Hz rTMS (1,500 pulses, 90 % RMT FDI) over the intact contralesional motor cortex. All subjects received 45 min of standard task-oriented upper-limb exercises. Outcome measures included dexterity (JHFT, nine hole peg test [NHPT], BBT), force, interhemispheric inhibition and corticospinal excitability and were assessed, prior to, after and for 3 months after the end of treatment. Indeed, contralesional 1Hz rTMS was shown to increase M1 excitability of the affected hemisphere; the effect was stable with rTMS-PT, but gradually declined after PT-rTMS. In addition, while both groups receiving real rTMS improved to a similar degree with untrained pinch and power-grip force measures when compared to sham stimulation, the rTMS-PT group showed bigger and more lasting improvements with dexterity measures compared to PT-rTMS. These findings indicate that priming PT with inhibitory rTMS (rTMS-PT) is more potent to rebalance motor excitability and enhance training-induced functional improvement among chronic stroke patients with mild motor impairment than the reverse order (PT-rTMS).

Taking together, the presented data indicates the potential of contralesional M1 1 Hz rTMS for motor recovery in stroke patients, an interpretation that is further supported by meta-analyses (as described below) showing moderately sized effect sizes. There is, however, a considerable variability of results with some positive and some negative trials. It seems clear that rTMS can act as priming and should preferentially be applied in conjunction with specific and efficacious arm rehabilitation training directly following stimulation. With regard to patient selection, patients with mild to moderate hand disability and subcortical stroke without concomitant severe diffuse white matter damage (leukoaraiosis) might have the best odds to benefit from contralesional M1 1 Hz rTMS. Saying this, the data is yet not conclusive to regard these criteria as exclusive.

While not systematically assessed, it remains an option to test the response to rTMS individually and decide on more extended therapy periods on that basis.

Intensities used varied from 90 to 120 % RMT FDI or APB, pulses given from 150 to 1,800 with a lower number of stimuli showing some effect, ten daily sessions being most frequently applied in positive trials with lasting effects.

4.2.1.2 High-Frequency rTMS of the Ipsilesional Motor Cortex (HF-rTMS)

Kim and colleagues (2006) showed as a ‘proof of principle’ in a cross-over laboratory experiment with single sessions of ipsilesional M1 sham or 10 Hz rTMS (160 pulses, 2 s trains at 10 Hz with 68 s inter-train interval, 80 % RMT FDI) paired

with 40 s practising a finger sequence task (during inter-train intervals) that 10 Hz rTMS can enhance excitability and short-term motor plasticity in mildly affected (chronic) stroke patients.

The effects of repeated HF-rTMS of the ipsilesional motor cortex in subacute stroke (<1 month) with mild to severe arm paresis on both arm motor recovery, as well as leg motor recovery, mobility and independence with activities of daily living, were investigated in a single blind RCT with 28 patients by Chang and colleagues (2010). A daily dose of 1,000 pulses of subthreshold ipsilesional 10 Hz rTMS combined with training (90 % RMT FDI, 5 s trains at 10 Hz with 55 s inter-train intervals consisting of 50 s reaching and grasping exercises and 5 s rest) was applied for 10 days within 1 month after onset of stroke, at the FDI hot spot or a corresponding mirror position of the non-lesioned hemisphere. Pre, post and 3 months follow-up assessments included motor clinical scales (Motricity Index arm and leg, Fugl-Meyer motor score, arm and leg, the box and block test [BBT], the functional ambulation category [FAC]) and an ADL scale (Barthel index, BI). A differential beneficial effect of real vs. sham HF-rTMS was documented for the Motricity Index, arm score only. Adverse effects were not observed. The findings indicate that subthreshold HF-rTMS of the ipsilesional arm motor cortex in subacute stroke patients can be safe and seems to enhance specifically (long-term) recovery of mild to severe arm paresis.

Sasaki and coworkers also included acute/subacute stroke patients comparing the effects of 5 days ipsilesional M1 10 Hz rTMS (1,000 pulses, 10 s trains at 10 Hz with 50 s inter-train interval, 90 % RMT), contralesional M1 1 Hz rTMS (1,800 pulses, 90 % RMT) and sham stimulation on finger tapping and grip strength. Again, adverse effects were not observed. For these subcortical ischaemic or haemorrhagic stroke patients, both types of real rTMS groups led to an increase in grip strength and finger tapping speed. Only for the 10 Hz rTMS group were changes in grip strength and tapping significantly different from the sham group, hinting to a better substantiated effect.

In summary, the data on HF-rTMS from RCTs is still limited, nevertheless indicating some clinical benefit. A clinical safety concern that might have prevented a more frequent use of HF-rTMS in clinical trials in motor stroke is its theoretically higher potential to induce epileptic fits (excitatory stimulation applied to the affected hemisphere) when compared to LF-rTMS to the contralesional M1 (inhibitory stimulation applied to the non-affected hemisphere). HF-rTMS of the ipsilesional M1 (1,000 pulses, 10 Hz, 80–90 % RMT FDI) was, however, not associated with any severe adverse event in the reported trials. It seemed to improve strength (grip strength, MI arm) and speeded selective movement (tapping) specifically and might induce long-term effects.

4.2.1.3 Theta-Burst Stimulation (TBS)

Talleli and colleagues (2007) compared single contralesional M1 cTBS and ipsilesional M1 iTBS with sham treatments (without motor training) on cortical excitability and motor performance measures in a small sample of 6 chronic stroke patients with mild arm paresis. Only ipsilesional iTBS improved motor behaviour

(shorter simple reaction time, SRT) of the paretic hand and changed physiological measures, i.e. increased excitability on stroke side, compared to sham stimulation. Grip strength and complex reaction time (CRT) were not differentially changed. cTBS reduced transiently motor-evoked potentials (MEP) of the healthy hand. The small sample size, number of stimuli (cTBS-300) and lack of training combined with stimulation are limitations of this laboratory experiment. The data suggests effects of both iTBS and cTBS without a clear therapeutic indication.

Among ten mild to moderately hemiparetic patients with chronic subcortical stroke, a single cTBS (reverse coil orientation) of the contralesional, a single iTBS (conventional orientation) of the ipsilesional M1 (600 stimuli, 90 % active motor threshold [AMT] FDI), or a sham stimulation was followed by 4×4 min practising precision grip movements (Ackerley et al. 2010). iTBS increased MEP amplitudes while the arm activity score ARAT was unchanged. After cTBS MEPs amplitudes as well as the ARAT score were on average reduced. While rather an experimental than a therapeutic setting (single TBS session), the example shows that TBS can affect MEPs and arm activity, that coil orientation and interaction with activity matter and that TBS can at times have a detrimental effect on function.

Given the network structure of sensorimotor control, it is conceivable that stimulation of different 'nodes' in sensorimotor networks could have differential effects on motor learning (Platz et al. 2012a, b) and motor recovery. Meehan and coworkers (2011) asked 12 chronic stroke patients with mild to moderate arm paresis to practise a serial target task (STT) for 3 days while receiving a sham or cTBS stimulation to either the contralesional M1 or S1 a couple of minutes before starting to practise. Both real cTBS groups showed bigger improvements with both the practised STT and with regard to completion time of the Wolf motor function test (WMFT) as compared to sham. Interestingly, the kinematics of the movements (movement time, maximal velocity, acceleration and deceleration) showed a bigger practice effects after contralesional M1 cTBS as compared to contralesional S1 cTBS, while movement initiation time and time to complete the WMFT tasks showed bigger improvements after cTBS to S1. Accordingly, different aspects of sensorimotor control of stroke patients might differentially be influenced by neuronavigated cTBS of either the contralesional S1 or M1.

Talelli and colleagues (2012) conducted a randomised sham-controlled trial involving 41 chronic stroke patients with mild to moderate hand motor deficits and blinded assessment. For 10 daily sessions all patients received strength training for wrist, fingers and thumb of the paretic hand as well as repetitive grasp and task practice including reaching. The training was primed by either sham stimulation, ipsilesional iTBS or contralesional cTBS at the FDI hot spot. Overall small but sustainable improvements were corroborated and shown to outlast the training period at least until 30 days later (NHPT, JHFT, grip strength [not pinch grip]; goal attainment scale [GAS] and VAS (patient satisfaction) assessed after treatment only). The training effects were, however, small and below the preset level of clinical significance (set at 10 % of each test's maximum). No effects of either iTBS or cTBS as compared to iSham or cSham could be corroborated. Thus, in this clinical situation of chronic stroke patients with mild hand and arm paresis who received a

specific training for 10 days, iTBS or cTBS priming was not beneficial. TBS seems therefore not to have induced an (purely) additional effect on motor improvement; any potential modifying effect might not have become observable giving the small effects of training itself.

Sung and coworkers investigated the effects of a combined first inhibitory than excitatory treatment course in stroke patients in the late subacute/early chronic phase (<1 year). Randomly assigned four groups participated in 20 daily sessions (4 weeks), receiving during the first 10 days (1st course) either real contralesional M11Hz rTMS or sham, followed by another 10 days (2nd course) with either real ipsilesional M1 iTBS or sham. The groups receiving either or both rTMS courses had bigger improvements on various motor outcome measures (WMFT, FM arm, finger tapping and reaction time) than the group receiving sham only. The group receiving both 1 Hz rTMS and then iTBS had bigger improvements (WMFT and RT) than the groups receiving one rTMS course (1Hz rTMS or iTBS). Motor map area decreased contralesionally after 1 Hz rTMS and was enlarged ipsilesionally after iTBS. Results were not modified by the factors cortical versus subcortical or ischaemic versus haemorrhagic stroke. It can be concluded that either 2 weeks of contralesional M1 1 Hz rTMS or ipsilesional M1 iTBS produced motor map area changes and motor improvements in these subacute to early chronic ischaemic or haemorrhagic stroke patients, with the prolonged/combined treatment producing substantially bigger behavioural effects.

In a consecutive double-blind RCT with 48 subacute ischaemic stroke patients with moderate to severe arm paresis (MRC ≤3), Wang and colleagues (2014) observed that both a sequence of 2 weeks contralesional M1 1 Hz rTMS followed by 2 weeks ipsilesional M1 iTBS as well as the reverse sequence produced motor map area changes and substantial and sustainable motor improvements (MRC, FM arm, WMFT) compared to sham. Motor recovery was, however, considerably bigger after the sequence of first 10 daily session contralesional M1 1 Hz rTMS followed by ipsilesional M1 iTBS (appr. 50 % improvement after the intervention period and 60–70 % at 3 months post) compared to the reverse order (20–30 % improvement). The sham group showed only small improvements (<10 % on average) indicating that the applied physiotherapy itself was not very effective.

Taken together, neither the inhibitory protocol cTBS when applied to the contralesional M1 nor the excitatory iTBS when applied to the ipsilesional M1 had effects on motor control and recovery been consistent across trials. Further, any specific effect on sensorimotor control in stroke patients with arm paresis could be modified by the stimulation target, e.g. contralesional M1 or S1 for cTBS. Most interesting clinically are the two RCTs from Taiwan (Sung et al. 2013; Wang et al. 2014) where a substantial number of stroke patients received combined rTMS and PT sessions over a total of 4 weeks. The prolonged combination of rTMS with 10 daily sessions of contralesional 1 Hz rTMS, followed by 10 daily sessions of ipsilesional M1 iTBS, led to the best observed, substantial and long-term motor recovery (50–70 % improvement compared to <10 % in the sham only control group). These results suggest that a prolonged priming of arm training both with a course of contralesional inhibitory and then ipsilesional excitatory rTMS might enhance motor recovery in subacute stroke patients.

4.2.1.4 Recovery of Gait

Chieffo and colleagues (2014) assessed the safety and efficacy of bilateral, excitatory, high-frequency rTMS over the lower limb cortical motor representation in 10 persons with chronic (>6 months) subcortical MCA stroke who were able to walk independently short distances (with aids if necessary). Each subject received both real and sham rTMS in a random sequence. The 2 rTMS cycles (real or sham) were composed of 11 sessions each, administered over 3 weeks and separated by a 4-week washout period. To reach the lower limb cortical motor areas, deeply located in the mesial cortical surface of the hemispheres, they delivered rTMS using a 'Hesed coil' (H-coil), which is designed to effectively stimulate at about a depth of 3–5 cm below the skull. HF-rTMS (30 trains at 20 Hz, 60 s inter-train interval, 1,500 pulses, 90 % RMT of either TA or 82 % max. stimulator output) was not specifically paired with motor exercises. Prior and after each treatment period and at a 4-week follow-up the Fugl-Meyer, leg motor score was assessed along with a 10 m walk test (10MWT) assessing gait velocity and a 6-min walk test (6MWT) measuring endurance. No adverse effects were observed. Superiority of improvement in favour of the real rTMS both after the treatment period and at follow-up 4 weeks later was documented for the Fugl-Meyer, leg motor score (only). The data suggest a potential of high-frequency rTMS delivered with the H-coil to both leg motor cortices for improving lower limb motor function in chronic ambulatory MCA stroke patients.

4.2.2 Meta-analyses

The systematic review and meta-analysis by Adeyemo and colleagues (2012) focused on treatment effects of rTMS (no TBS included) and tDCS on motor function after stroke and included studies published within 10 years, written in English, and involving at least three patients. Fifty studies with a total of 1,282 stroke subjects and an average age of 58.46 years were included. Only six studies included subacute patients, five acute patients. Thus, the evidence was largely covering chronic stroke patients.

No major adverse effects have been reported. The side effects reported were tingling, headache, dizziness, itching and increase in anxiety.

Most of the studies used small sample sizes. Thirty-six (72 %) studies used rTMS (the others tDCS). Most of the rTMS studies were controlled and used sham stimulation or active control stimulation (77.7 %); the techniques used were different: active coil placed on the vertex; active coil, with an angle of application of 90°; and sham coil, which induces no magnetic field.

A majority of the results was positive with bigger improvements after active rTMS compared to the control stimulation, with the exception of three articles (Lomarev et al. 2007; Malcolm et al. 2007; Pomeroy et al. 2007). The results from a fixed effects model revealed a significant pooled effect size of 0.584 (95 % CI, 0.440, 0.729) in favour of rTMS/tDCS. The random effects model showed similar results 0.590 (pooled effect size, 95 % CI, 0.421, 0.760). The authors found no evidence of publication bias.

The effect size was not influenced by age. Similarly, no robust effect of gender was reported with a slight hint towards bigger effects with a higher male proportion in study samples. Given the low number of studies investigating acute or subacute stroke patients, chronicity as a potential modifying factor could not rigorously be analysed. The (positive) evidence regarding long-term effects had been limited.

The analysis did, however, demonstrate a significantly increased effect size when stimulation was applied to subcortical strokes versus the mixed strokes. It is conceivable that a subcortical stroke that preserves the cortex allows rTMS to influence the recovery of functionally relevant cortical network activity and connectivity.

In conclusion, this review provides a broad picture including all sorts of rTMS approaches in motor stroke, and it gives an indication that there is a potential for a clinical benefit with an overall moderate effect size. The type of studies included (e.g. some laboratory, some clinical trials, not all randomised, limited blinded assessment, various stimulation types, limited information on long-term effects) all make it difficult to draw firm conclusions on whom to treat when, how and for how long and how to combine rTMS with training.

The systematic review and meta-analysis by Hao and colleagues (2013) assess the efficacy and safety of rTMS for improving function in people with stroke. The authors included only RCTs, trials comparing rTMS therapy with sham therapy or no therapy, and excluded trials that reported only laboratory parameters. The included studies could target motor function with rTMS as well as visual perception (neglect), aphasia or depression, all reflecting some type of 'function'. Primary outcomes were activities of daily living (ADL), such as the Barthel index, the Functional Independence Measure and the modified Rankin Scale. Secondary outcomes were upper and lower limb motor function, any other improvement of impairment, adverse events, death or disability. Compared to the systematic review of Adeyemo and colleagues (2012), this review was methodologically more focused (only rTMS, only RCTs), but less focused regarding the target symptoms: The outcome measures were primarily addressing effects on ADLs, and only as secondary measures motor and cognitive function, or mood. Further, brain targets for rTMS were not restricted to M1. Hao and colleges included 19 trials involving a total of 588 participants in their review.

The quality of reporting in the trials in general was considered poor. The funnel plots showed a slightly asymmetrical funnel distribution, which indicated likely publication bias.

Eight trials with a total of 173 participants reported motor function of the affected extremities. However, data for a meta-analysis were available from only four trials and 73 participants (42.2 %, 73/173) (Fregni et al. 2006; Khedr et al. 2009; Malcolm et al. 2007; Pomeroy et al. 2007). This meta-analysis showed that rTMS treatment was not associated with a significant improvement in motor function (SMD 0.51, 95 % CI −0.99 to 2.01). However, there was statistically significant heterogeneity between trials ($I^2 = 87.6$ %).

Eight trials reported that there were no adverse effects. Six trials reported adverse outcomes: eight transient or mild headaches (2.4 %, 8/327) were observed in the rTMS group; one participant reported an increase in anxiety (0.3 %, 1/327); two

participants had single episodes of neurocardiogenic syncope (0.6 %, 2/327) with their initial exposure to rTMS; an exacerbation of initial insomnia was observed in one participant (0.3 %, 1/327); and local discomfort at the site of the stimulation. Five trials made no mention of adverse outcomes.

In summary, this systematic review and its meta-analyses highlights the methodological quality restrictions in some of the rTMS trials and asks for methodologically more rigorous research in the field. It does, however, not focus on motor recovery after stroke and therefore its applicability in this domain is limited.

The systematic review and meta-analysis by Hsu and co-authors (2012) investigated (more) specifically the effects of repetitive transcranial magnetic stimulation (rTMS) on upper limb motor function in patients with stroke. They included only RCTs, studies needed to have a focus on upper limb function after stroke (had to recruit at least six patients and to be written in English).

Eighteen studies were identified. In total, 392 patients with stroke were included, and 370 were re-evaluated postintervention. Three studies recruited patients in the acute phase, three studies in the subacute phase and seven other studies investigated patients with chronic stroke. Regarding lesion sites, six trials recruited patients with subcortical stroke only, whereas the other studies recruited patients with both cortical stroke and/or subcortical stroke.

Thirteen of the 18 studies reported adverse effects. Only one trial found adverse events, including two patients with headaches, one patient with increased anxiety and one patient with increased fatigue.

The meta-analysis of motor outcome showed a statistically significant mean effect size of 0.55 (95 % CI, 0.37–0.72; $P<0.01$).

Sub-analyses revealed the following results (compare Fig. 4.2): The analysis revealed a mean effect size of 0.69 (95 % CI, 0.42–0.95; $P<0.001$) for patients who received low-frequency rTMS; the mean effect size for patients who received high-frequency rTMS was 0.41 (95 % CI, 0.14–0.68; $P<0.01$). The subgroup mean effect size for acute stroke was 0.79 (95 % CI, 0.42–1.16; $P<0.001$), 0.63 (95 % CI, 0.18–1.08; $P<0.01$) for subacute stroke and 0.66 (95 % CI, 0.31–1.00; $P<0.001$) for chronic stroke. The mean effect size for subcortical lesions was 0.73 (95 % CI, 0.44–1.02; $P<0.001$), for nonspecified lesion sites 0.45 (95 % CI, 0.23–0.67; $P<0.001$).

The effect of rTMS on cortical excitability was evaluated based on resting motor threshold data (RMT) from the affected hemisphere in six trials. The meta-analysis for RMT showed a non-significant mean effect size of 0.30 (95 % CI, −0.09 to 0.68; $P>0.05$).

For all mentioned analyses, there was no heterogeneity across the studies.

Although the above-mentioned subgroup analysis indicated a greater beneficial effect of contralesional low-frequency rTMS compared with ipsilesional high-frequency rTMS, the TBS studies revealed that ipsilesional iTBS may be more helpful for motor recovery (no formal analysis performed due to limited data).

From this focused meta-analysis including RCTs that specifically assessed the effects of rTMS (including TBS) on upper limb motor function after stroke, it can be concluded that the intervention tested has a moderate positive effect (mean effect size 0.55). There are factors that are associated with somewhat higher effect sizes

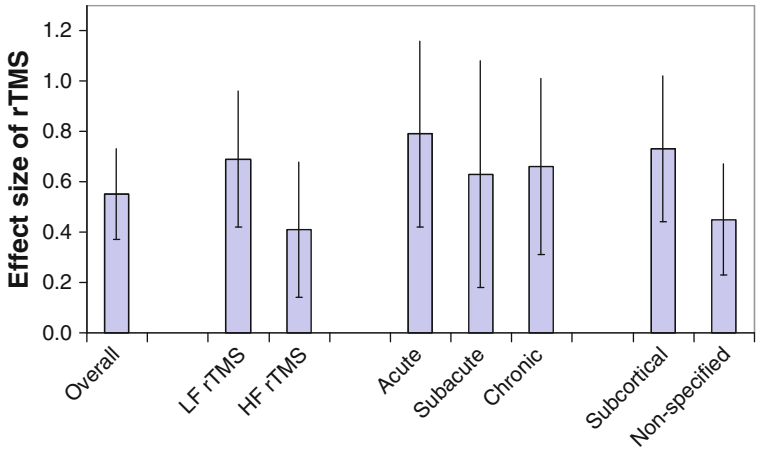

Fig. 4.2 Effect sizes for rTMS in arm motor rehabilitation after stroke according to a meta-analysis by Hsu et al. (2012). Standardised effect sizes and 95 % confidence intervals based on data from 18 trials and 370 patients are presented. Because effect sizes may be influenced by sample sizes and effects may be overestimated in studies with low numbers of patients, a weighting factor was applied that gave more weight to studies with larger samples. Finally, the mean effect sizes were obtained after combining the weighted effect size of each study. Absolute effect sizes that ranged from 0.2 to 0.49 were considered to be small, and a value of 0.5 was likely to be clinically meaningful (Sloan et al. 2005)

(subcortical stroke, acute stroke, contralesional LF-rTMS) and yet a positive effect of rTMS could still be corroborated in subgroups without these 'positive' factors, i.e. with stroke involving the cortex, chronic stroke, ipsilesional HF-rTMS. Long-term effects are, however, not well known yet. Side effects were mild and rare.

A further meta-analysis of moderate- to high-quality RCTs (published in English) by Le and colleagues (2014) investigated the effects of rTMS specifically on hand function after stroke (as well as cortical excitability and any adverse events). Eight studies with a total of 273 patients were included; all subjects of the included trials had subcortical strokes.

Few adverse events were observed. The meta-analysis corroborated a positive effect of rTMS on finger motor ability (SMD 0.58, 95 % CI, 0.12–1.04; $P=0.01$) and hand function (SMD −0.82, 95 % CI, −1.30 to −0.33; $P=0.0009$). Changes of neurophysiological measures (MEP, RMT) by rTMS were not substantiated nor were motor performance changes for the unaffected hand (SMD −0.01) when the contralesional M1 was inhibited.

4.2.2.1 Best Evidence Synthesis and Its Relevance for Clinical Decision Making

What is the current state of the art regarding rTMS in motor rehabilitation after stroke?

A substantial number of RCTs have been published on the topic (compare Tables 4.1, 4.2, 4.3 and 4.4). Most address arm function, one gait. The data on gait

Table 4.1 LF-rTMS of the contralesional motor cortex (LF-rTMS)

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Avenanti et al. (2012)	DB RCT, 30 subjects Chronic unilateral stroke sparing M1 Mild paresis	Real or sham rTMS before or after 45 min task-specific arm training 10 daily sessions, 1 Hz rTMS (1,500 pulses, 90 % RMT FDI), contralesional M1	rTMS increased M1 excitability of the affected hemisphere, stable effect with rTMS-PT (3 months), gradual decline after PT-rTMS Bigger and more lasting improvements with dexterity after rTMS-PT compared to PT-rTMS Conclusion: rTMS-PT is more potent to enhance training-induced functional improvement among chronic stroke patients with mild motor impairment than PT-rTMS
Conforto et al. (2012)	SB RCT 30 subjects Subacute (5–45 days) unilateral stroke (ICA) Hand paresis	Real or sham rTMS before or after 60 min training 10 daily sessions, 1 Hz rTMS (1,500 pulses, 90 % RMT APB), contralesional M1	JTHF and pinch force improved only in the real rTMS group (inter-group difference n.s.); FM arm, MRS improvement in both groups (no inter-group difference) Conclusion: no additional benefit corroborated (underpowered study)
Emara et al. (2009, 2010)	RCT 60 subjects Subacute or chronic unilateral stroke (≥1 month) Mild to moderate hand disability	Real (1 Hz or 5 Hz) or sham rTMS combined with PT 10 daily sessions 1 Hz rTMS (150 pulses, 110–120 % RMT APB), contralesional M1 5 Hz rTMS (750 pulses, 80–90 % RMT APB), ipsilesional M1 rTMS dosage (pulses) was low	(2010) Both contralesional 1Hz and ipsilesional 5 Hz rTMS lead to comparable and lasting (12 weeks FU) improvements in finger tapping, Activity Index and modified Rankin Scale while sham did not (2009) Patients with TACS and severe leukoaraiosis had the least favourable outcome. Cortical involvement prohibited effects of contralesional 1Hz rTMS Conclusion: both 1 and 5 Hz rTMS lead to lasting effects on recovery in a mixed subacute to chronic stroke patient population with mild to moderate hand disability. Small dosages (pulses) might suffice. Effects of contralesional 1 Hz rTMS may depend on an intact M1 of the lesioned hemisphere
Etoh et al. (2013)	DB cross-over RCT 18 subjects Chronic first or second unilateral ischaemic or haemorrhagic stroke (>5 month) Mild to moderate UL deficits	1 Hz or sham rTMS combined with 40 min PT (repetitive Facilitating exercises, RFE) 10 daily sessions 1 Hz rTMS (240 pulses, 90 % RMT APB), contralesional M1 rTMS dosage (pulses) was low	Gains with the FM arm, ARAT and STEF (timed measure of dexterity) were corroborated only for the real rTMS period, being statistically sign. Different from the sham period for the ARAT scores Conclusion: short-duration contralesional M1 1Hz rTMS combined with repetitive arm training improves motor function in chronic stroke patients with mild to moderate deficits

(continued)

Table 4.1 (continued)

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Liepert et al. (2007)	Laboratory cross-over trial 12 subjects, acute subcortical ischaemic stroke (<14 days) Mild UL deficits (MRC 4)	Single session (same day, 30 min delay), Contralesional M1 sham or 1 Hz rTMS (1,200 pulses, 90 % RMT FDI) No training	After contralesional 1 Hz rTMS performance of the affected hand improved with the NHPT, grip force was unaffected Conclusion: 1 Hz rTMS to the contralesional M1 can enhance finger dexterity in mildly affected patients with acute subcortical stroke
Mansur et al. (2005)	Laboratory cross-over trial 10 subjects, ischaemic stroke (<1 year) Mild UL deficits	Single session (same day, 60 min delay) Contralesional M1 sham or M1 or PMC 1 Hz rTMS (600 pulses, 100 % RMT) No training	After contralesional M1 1 Hz rTMS improved peg tasks (Purdue Pegboard), sRT and cRT performance (but not finger tapping) compared to sham. Effects after PMC 1 Hz rTMS were not sign Conclusion: 1 Hz rTMS to the contralesional M1 (more than PMC) can enhance dexterity in mildly affected stroke patients
Pomeroy et al. (2007)	Laboratory trial 24 geriatric subjects, subacute MCA stroke (<13 weeks) Incomplete UL deficits	8 days with treatment session Random assignment to 4 groups: rTMS/placebo and VMC/placebo (factorial design) 1 Hz rTMS (200 pulses, 5×40 with 3 min interval, 120 % RMT) Novel task training for 15 min (cranked wheel turning) following rTMS and VMC	Combined real rTMS and real VMC increased MEP amplitude (biceps and triceps) (trend, no test of sign.) The placebo group (rTMS + VMC placebo) showed numerically the biggest improvement in ARAT scores (no test of sign.) 1 subject reported headaches after rTMS Conclusions: no clinically relevant conclusions to be drawn
Seniów et al. (2012)	DB RCT 40 subjects, subacute (≤3 months) Hemispheric stroke Moderate arm paresis (NHISS 1–3) A priori power calculation: 129 pts	Real or sham rTMS prior to 45 min PT as Bobath therapy 15 daily sessions 1 Hz rTMS (1,800 pulses, 90 % RMT FDI), contralesional M1	WMFT, FM arm, NIHSS: comparable improvement post therapy and 3 months later in both groups (no difference) Cortical structures were involved in 26/40 subjects; a subpopulation analysis with subcortical strokes showed a similar result Conclusion: no additional benefit corroborated (underpowered study; the Bobath therapy's efficacy might be questioned)

Takeuchi et al. (2005)	Laboratory trial 20 subjects, chronic subcortical ischaemic stroke (≥6 months) Mild to moderate deficits	Single session Randomly assigned to contralesional M1 sham or 1 Hz rTMS (1,500 pulses, 90 % RMT FDI) rTMS/sham given after training for 8 days with ceiling	After contralesional 1 Hz rTMS, but not sham, reduced MEPs, reduced transcortical inhibition duration and increased acceleration (but not force) with a pinch task was further improved shortly (beyond training) (not at 30 min post rTMS) Conclusion: a single session of 1 Hz rTMS to the contralesional M1 can change cortical excitability and transcortical inhibition inducing short-lived effects on motor performance in subcortical stroke
Takeuchi et al. (2008)	Laboratory trial 20 subjects, chronic subcortical ischaemic stroke (≥6 months) Mild to moderate deficits	Single session Randomly assigned to real or sham rTMS Contralesional M1 sham or 1 Hz rTMS (1,500 pulses, 90 % RMT FDI) Followed by motor training with a pinching task	After contralesional 1 Hz rTMS, but not sham, MEPs transiently decreased in the stimulated and increased the affected hemisphere while acceleration and force (after training only) with a pinch task persistently increased (still observed after 1 week) Conclusion: a single session of 1 Hz rTMS to the contralesional M1 can transiently change cortical excitability and if followed by a training can induced bigger and lasting motor training effects (pinching task) in chronic subcortical stroke
Theilig et al. (2011)	SB RCT 21 subjects, subacute to chronic, first ischaemic hemispheric stroke Severe sensory and/or hand motor deficits	Real or sham rTMS prior to 20 min EMG-triggered neuromuscular electrical stimulation (EMG-NMES; EDC/ECR) 10 daily sessions 1 Hz rTMS (900 pulses, 100 % RMT FDI), contralesional M1 Sham rTMS (identical, but with zero stimulator output)	Patients were mainly subacute (18/21<6 months); 20/21 had MRC 0 for wrist and finger extensors No adverse effects were observed WMFT: comparable improvement post therapy in both groups (appr. 20 %) (no difference) Tardieu (spasticity) and MEPs: no significant effects over time (or by intervention) Conclusion: in (mainly subacute) stroke patients with severe paresis (and somatosensory deficits) of the hand function improved after 2 weeks of EMG-NMES without any additional benefit of contralesional M1 1Hz rTMS

Table 4.2 High-frequency rTMS of the ipsilesional motor cortex (HF-rTMS)

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Chang et al. (2010)	SB RCT 28 subacute stroke patients (<1 month), Mild to severe	Real or sham rTMS intermingled with reaching and grasping exercises 10 daily sessions, 10 Hz rTMS (1,000 pulses, 5 s trains at 10 Hz with 55 s inter-train interval, 90 % RMT FDI), ipsilesional M1	Bigger improvement (pre, post, 3 months) for real HF-rTMS with MI-arm; no superiority for other arm, leg, mobility, or ADL measures. No adverse effects Conclusion: subthreshold 10 HF-rTMS of the ipsilesional M1 in subacute stroke patients can be safe and enhances specifically some aspects of (long-term) recovery of mild to severe arm paresis (strength)
Kim et al. (2006)	Laboratory cross-over trial 15 subjects, subacute to chronic ischaemic or haemorrhagic stroke (>3 month) without M1 damage Mild UL deficits	Two sessions (1 week interval), M1 sham or 10 Hz rTMS (160 pulses, 2 s trains at 10 Hz with 68 s inter-train interval, 80 % RMT FDI), ipsilesional M1 Intermingled with 40 s finger sequence learning task (during inter-train interval)	Gains in movement accuracy and time (finger sequence task) were bigger after 10 Hz rTMS; in addition, there was an increase in MEP amplitudes (after real rTMS) Conclusion: 10 Hz rTMS to the ipsilesional M1 enhances excitability and short-term motor plasticity in mildly affected stroke patients
Sasaki et al. (2013)	SB RCT 29 subjects, acute/subacute subcortical ischaemic MCA or haemorrhagic stroke not involving the cortex	5 daily sessions, real or sham rTMS 1 Hz rTMS (1,800 pulses, 90 % RMT), contralesional M 10 Hz rTMS (1,000 pulses, 10 s trains at 10 Hz with 50 s inter-train interval, 90 % RMT), ipsilesional M1 40–80 min rehabilitative therapy per day	Both real rTMS groups showed an increase in grip strength and finger tapping speed. Only for the 10 Hz rTMS group were changes in grip strength and tapping significantly different from the sham group No adverse effects were reported Conclusions: both ipsilesional 10 Hz and contralesional 1 Hz M1-rTMS improve motor function in (apparently mildly) affected acute/subacute subcortical ischaemic or haemorrhagic stroke patients; the effect after 10 Hz could more rigorously be substantiated

Table 4.3 Effects of theta-burst stimulation (TBS) of the motor cortex on motor function

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Ackerley et al. (2010)	DB cross-over RCT 10 subjects Chronic subcortical stroke (>5 month) Mild to moderate UL deficits	Three sessions Sequence randomly assigned to iTBS to ipsilesional M1, cTBS to contralesional M1, or sham TBS to either M1 TBS (600 pulses, 90 % AMT non-paretic FDI), reverse coil orientation was used for cTBS Followed by practising 4×4 min precision grip movements (15 min after TBS)	Ipsilesional M1 excitability increased after iTBS but decreased after cTBS Paretic-hand grip-lift kinetics improved after TBS (only) ARAT scores deteriorated when training followed cTBS Conclusion: TBS and training led to task-specific improvements in grip-lift in chronic subcortical stroke patients. Arm activity (ARAT) deteriorated, however, after contralesional M1 cTBS
Meehan et al. (2011)	Laboratory trial 12 subjects, chronic ischaemic or haemorrhagic stroke (≥12 months), Mild to moderate UL deficits (FM arm >14)	Three days of neuronavigated stimulation 3 groups randomised either to sham or cTBS (600 pulses, 80 % AMT ECR) to either contralesional M1 or S1 stimulation Followed by practising a serial target task (STT) 4×150 trials	cTBS of both the contralesional M1 and S1 induced effects that were superior to sham when assessed 1 day after stimulation (STT: initiation time, MT, vel., acc., dec.; WMFT time) with differences of the magnitude of effects between cTBS-S1 and cTBS-M1: cTBS-M1 – larger decreases in peak velocity and peak acceleration; cTBS-S1 – larger reductions in time to initiate movement and time to complete the WMFT Conclusion: both contralesional M1 and S1 can be targets for cTBS in motor recovery with differential effects on motor control aspects

(continued)

Table 4.3 (continued)

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Sung et al. (2013)	DB RCT 54 subjects, subacute to early chronic (3–12 months) ischaemic or haemorrhagic hemispheric stroke	20 daily sessions (4 weeks), 10 days (1st course) real 1 Hz contralesional M1 rTMS or sham, followed by 10 days (2nd course) real iTBS ipsilesional M1 or sham 1 Hz rTMS (600 pulses, 90 % RMT FDI), contralesional M1 iTBS (600 pulses, 2 s trains of 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT FDI), ipsilesional M1 Conventional rehabilitative therapy each day (OT & PT)	The groups receiving either or both rTMS courses had bigger improvements than sham only (WMFT, FM arm, finger tapping and reaction time). The group receiving both 1 Hz rTMS and then iTBS had bigger improvement (WMFT and RT) than the groups receiving one rTMS course only. Motor map area decreased contralesionally after 1 Hz rTMS and was enlarged ispilesionally after iTBS Results were not modified by factors cortical/subcortical or ischaemic/haemorrhagic Conclusions: either 2 weeks contralesional M1 1 Hz rTMS or ipsilesional M1 iTBS produce motor map area changes and motor improvements in subacute to early chronic ischaemic or haemorrhagic stroke patients, with the prolonged/combined treatment producing bigger effects
Talelli et al. (2007)	Laboratory trial 6 subjects, chronic ischaemic stroke (≥12 months), cortical and/or subcortical damage Mild UL deficits	Five sessions: Three sessions with either sham stimulation, ipsilesional iTBS or contralesional cTBS and motor assessment Two sessions with either iTBS or cTBS and electrophysiological measurements iTBS (600 pulses, 2 s trains of 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT), ipsilesional M1 cTBS (300 pulses, 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT), contralesional M1	Only ipsilesional iTBS improved motor behaviour (shorter SRT) and changed physiological measures (increased excitability on stroke side) of the paretic hand. Grip strength and CRT were not differentially changed. cTBS reduced transiently MEPs of the healthy hand Conclusion: a single session iTBS of the ipsilesional hemisphere can increase cortical excitability and motor performances (SRT). Behavioural cTBS effects were not substantiated in this small sample

Talelli et al. (2012)	SB two-centre RCT 41 subjects, chronic ischaemic stroke (≥12 months), cortical and/or subcortical damage Mild to moderate hand deficits without severe spasticity (AS <2) If no ipsilesional MEP was present ($n=8$), random assignment was contralesional cTBS or sham only	10 daily sessions with either sham stimulation ($n=16$), ipsilesional iTBS ($n=13$) or contralesional cTBS ($n=12$) at the FDI hot spot followed by PT (strength training wrist/fingers/thumb, repetitive grasp and task practice including reaching) iTBS (600 pulses, 2 s trains of 3 pulses at 50 Hz repeated at 200 ms intervals, 20 trains of 10 bursts given with 8-s intervals, 80 % AMT FDI), ipsilesional M1 cTBS (600 pulses, 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT FDI), contralesional M1	No adverse effects were observed Primary outcome measures (JHFT, NHPT, grasp and pinch grip strength) assessed pre, post, at 30 days and 90 days (JHFT, NHPT); secondary outcome measures (GAS, AS, ROM, RASP) pre and post Overall small but sustainable improvements were corroborated (at least until 30 days; NHPT, JHFT, grip strength [not pinch grip]; below preset level of clinical significance [10 % of maximum]; GAS and VAS (patient satisfaction) at post). No effects of either iTBS or cTBS as compared to iSham or cSham could be corroborated Conclusion: 10 days of ipsilesional M1 iTBS or contralesional M1 cTBS failed to enhance the effects of a repetitive hand function training and mildly affects chronic stroke patients who had small benefits from the training
Wang et al. (2014)	DB RCT 48 subjects, subacute (2–6 months) ischaemic stroke Moderate to severe arm paresis (MRC ≤3)	20 daily sessions (4 weeks): Group A: 10 days (1st course) real contralesional M1 1 Hz rTMS, followed by 10 days (2nd course) real ipsilesional M1 iTBS Group B: reverse order of first and second course compared to group A Group C: sequence as group A with sham stimulation (only) 1 Hz rTMS (600 pulses, 90 % RMT FDI), contralesional M1 iTBS (600 pulses, 2 s trains of 3 pulses at 50 Hz repeated at 200 ms intervals every 10 s, 80 % AMT ipsiles. FDI), ipsilesional M1 Conventional rehabilitative therapy each day (1 h PT); during FU period twice per week	Compared to sham group A had bigger improvements at all assessment points (starting after the first course until 3 months post) in all assessments (MRC, FM arm, WMFT), group B only for MRC proximal and WMFT Group A had bigger changes over the second course (iTBS; prox. MRC, FM arm, WMFT) Group A had bigger improvements after the first course (FM arm, WMFT) and after the second course compared to baseline Both groups had similar and sustainable decrements (unaffected hemisphere, UH) and increments (affected hemisphere) in motor map areas, while group C had an opposite increment (UH) over time Conclusions: both the sequence of 2 weeks contralesional M1 1 Hz rTMS followed by 2 weeks ipsilesional M1 iTBS and the reverse sequence produced motor map area changes and substantial and sustainable motor improvements in subacute ischaemic stroke patients compared to sham. Motor recovery was bigger after 1 Hz rTMS –>iTBS (50 % after intervention 60–70 % at 3 months post) compared to the reverse order (20–30 %)

Table 4.4 Motor cortex rTMS to improve lower limb function

Reference	Study type and population	Intervention, comparison	Outcome measures, main results, conclusion
Chieffo et al. (2014)	DB cross-over RCT 10 chronic subcortical MCA stroke Ambulatory (with aids)	11 sessions (in 3 weeks), sham or real HF-rTMS (H-coil, bilateral leg M1, 30 trains at 20 Hz, 60 s inter-train interval, 1,500 pulses, 90 % RMT of either TA or 82 % max. stimulator output) No specific training	rTMS: superior improvement of FM, leg motor score post treatment and 4 weeks later; 10 MWT and MWT n.s. diff. between groups Conclusion: bilateral HF-rTMS of the leg motor cortices induces lasting improvement of lower limb function in ambulatory stroke patients

rehabilitation is still so limited that while being reported above it will not be included in this best evidence synthesis that consequently will address arm function only.

The general approach for arm motor rehabilitation after stroke has either been to 'enhance excitability' of the ipsilesional M1 (APB, FDI) by an excitatory rTMS (HF-rTMS or iTBS) or to 'reduce excitability' of the contralesional M1 (APB, FDI) by an inhibitory rTMS (LF-rTMS or cTBS). Either approach induced clinically relevant benefits as suggested by meta-analyses (Adeyemo et al. 2012; Hsu et al. 2012).

Inhibitory (I) and excitatory (E) stimulation protocols that had typically been used were:

- LF-rTMS (I) of the ipsilesional M1 (900–1,800 pulses, 1 Hz, 90–110 % RMT FDI or APB)
- cTBS (I) of the contralesional M1 (600 pulses, 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT FDI)
- HF-rTMS (E) of the ipsilesional M1 (1,000 pulses, 10 Hz, 5–10 s trains with 50–55 s inter-train interval, 80–90 % RMT FDI)
- iTBS (E) of the ipsilesional M1 (600 pulses, 2 s trains of 3 pulses at 50 Hz repeated at 200 ms intervals, 80 % AMT FDI)

Up to now there is no clear indication which approach might be superior. While one meta-analysis favoured contralesional LF-rTMS over ipsilesional HF-rTMS (Hsu et al. 2012), there is evidence that iTBS to the ipsilesional M1 could also be very effective, especially when preceded by a course of contralesional LF-rTMS (Sung et al. 2013; Wang et al. 2014). According to the latter two RCTs the combination of a 2-week course of contralesional LF-rTMS with a consecutive 2-week course of iTBS – and thus of the two approaches – resulted in remarkable long-term arm motor recovery in subacute stroke patients.

Typical therapeutic courses applied 10 days of stimulation when one type of rTMS was applied; this could be used for a clinical orientation. Especially the above-mentioned combination over 4 weeks resulted in bigger effects than a 2-week course of either type of intervention. Thus, when feasible, more than 2 weeks of therapy and the described combination could be considered.

There is good reason to assume and indeed direct proof in one paper (Avenanti et al. 2012) that rTMS acts as a priming procedure and enhances training-induced motor recovery when applied immediately before (rather than after) training. As such it seems critical to combine rTMS with an arm training that is both specific and efficacious if one wanted rTMS to enhance (modify) training-induced plasticity. Saying this, it remains a possibility that rTMS does not enhance the most efficacious training methods since then a ceiling effect might neurophysiologically apply. While we do not have direct evidence for that, it is of interest to note that with the biggest clinical effects of rTMS (50–70 % improvement) there was only little benefit from training only (<10 %).

Since sensorimotor control involves complex networks in the brain, M1 is not the only target for priming training-induced changes. Other areas such as PMC, SMA or S1 could equally be candidates. Their inhibitory stimulation has been shown to influence training-induced motor learning specifically regarding various motor tasks and affordances (Platz et al. 2012a, b). While there is preliminary evidence for the relevance of such ideas in a stroke patient study (Meehan et al. 2011), there is not yet sufficient data to base clinical decision on it.

Patient characteristics as covariates or modifiers of rTMS effects on motor recovery after stroke are of high clinical importance. Such knowledge could help to guide which patient to treat with rTMS and when.

The data collated and the meta-analyses speak against a big effect of age on the response to rTMS. Accordingly, patients would not have to be excluded from a stimulation therapy based on their age.

What matters is rather the individual biology. Severe diffuse white matter disease of the brain (leukoaraiosis) is associated with a reduced response to rTMS therapy on motor stroke. Gender effects are small, potentially favouring the male gender somewhat.

M1 lesion prevents ipsilesional M1 HF-rTMS or iTBS since no substrate for this therapy is left over. Contralesional M1 LF-rTMS seems best to work in patients with subcortical strokes leaving their cortex intact; but this does not imply that patients with cortical involvement could not benefit from this type of stimulation.

There was no clear indication that haemorrhagic strokes respond less well to rTMS as compared to ischaemic stroke. One might, however, keep in mind that there is a somewhat higher risk of haemorrhagic stroke to develop symptomatic epilepsy (Burneo et al. 2010).

Chronicity after stroke is a relevant factor in motor recovery with the biggest recovery rates occurring within the first 3 months. Effects of rTMS have been demonstrated for acute, subacute and chronic stages after stroke with the early phase showing somewhat bigger effects (Hsu et al. 2012).

The brain-derived neurotrophic factor (BDNF) gene often shows a single nucleotide polymorphism that is thought to influence synaptic plasticity and the modulatory effects of rTMS on motor cortex excitability. In a sample of 44 stroke patients with hemiparesis, BDNF genotyping was performed via PCR assays; rTMS was applied over the ipsilesional M1 at 10 Hz with 1,000 pulses/day for 10 days (Chang et al. 2014). Arm motor improvement was shown immediately after and 2 months after rTMS in both the Val/Val ($n=9$) and the Met allele group ($n=35$). The Val/Val

group improved, however, to a greater extent than the Met allele group indicating that the BDNF gene polymorphism negatively influences the effect of ipsilesional M1 HF-rTMS on arm motor recovery in stroke patients.

While long-term effects of rTMS therapy have been shown in motor stroke, the database regarding these effects is still limited.

Taken together, there is a substantial database indicating that the above-mentioned rTMS applications are safe and not associated with (a high frequency of) worrisome or serious adverse events when the conventional safety guidance recommendations are applied (e.g. no history of epileptic seizure, no incorporated ferromagnetic devices, stimulation protocols according to international safety recommendations) (Rossi et al. 2009).

Given this low risk profile and the demonstrated clinical benefits (Andrews et al. 2013), there is reason to apply rTMS therapy in stroke patients with motor deficits, especially arm paresis and preferable in centres experienced with this type of therapy. The intervention that had best been investigated is contralesional M1 LF-rTMS.

While the most focused meta-analysis by Hsu and co-authors (2012) reported an overall effect size of 0.55 on average for rTMS therapies in arm motor rehabilitation after stroke and thus could support a 'strong' recommendation, the presented heterogeneity of results across RCTs as reported above makes a 'weak' recommendation in favour of rTMS more appropriate (according to GRADE, Guyatt et al. 2008; Andrews et al. 2013): The recommendation in favour of rTMS in arm motor rehabilitation is qualified with the above-stated explanations that should individually be taken into consideration.

Accordingly, any individual therapeutic decision should be based on both the individual's health circumstances and reflected against the body of clinical evidence as described above.

If rTMS therapy is applied clinically in motor rehabilitation after stroke, it would be warranted to collect clinical data in observational studies to help create a bigger database for clinical reasoning.

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rTMS in Dysphagia After Stroke

5

Jin-Woo Park

Abstract

Dysphagia is a commonly documented morbidity after stroke and has been associated with an increased risk for pulmonary and nutritional complications and even mortality. The dysphagia therapy focused on compensatory and rehabilitative strategies for many years; unfortunately, there is a paucity of evidence for these methods. Recently, a new approach using noninvasive cortical stimulation which modulates cortical excitability is being applied to help the neurologic recovery after a stroke and a few studies applied repetitive transcranial magnetic stimulation (rTMS) on post-stroke dysphagia, which led to a significantly greater improvement in swallowing function. There remains uncertainty on which stimulation method (frequency, site, and amount) is best; therefore, more research should be conducted in the future.

5.1 Introduction

Dysphagia is a commonly documented morbidity that follows stroke, and its reported incidence is widely discrepant, ranging between 27 and 64 %. (Barer 1989; Gordon et al. 1987; Mann et al. 2000; Odderson et al. 1995; Smithard et al. 1996; Wolfe et al. 1993) From a neuroanatomical perspective, unilateral strokes lead to dysphagia in 40 % of cases, bilateral lesions of the cerebral hemispheres in 56 %, brainstem lesions in 67 %, and combined lesions in 85 % (Broadley et al. 2003; Horner et al. 1991).

The presence of dysphagia has been associated with an increased risk for nutritional and pulmonary complications and even mortality. Alterations in the efficacy of deglutition cause malnutrition and/or dehydration in up to 25 % patients, and impaired safety of swallowing increases the risk for aspiration pneumonia (Martino

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et al. 2005). Malnutrition after stroke is closely associated with poor outcome including death, dependency, and institutionalization (Davalos et al. 1996). Up to 20 % of patients with stroke suffer from early aspiration pneumonia, and it is one of the major causes of mortality during the first year after discharge (Hilker et al. 2003).

Swallowing assessments are generally split into bedside clinical examinations or instrumental investigations. Bedside examination remains the cornerstone of clinical practice in most hospitals. Clinicians, nurses, and speech and language therapists are taught to present small volumes of food or water to patients and to watch for signs of dysphagia and aspiration (DePippo et al. 1992). Among other signs, clinicians will look for loss of liquid from the mouth, dyspraxia, delayed pharyngeal/laryngeal elevation, coughing or throat clearing, breathlessness, and changes in voice quality after swallowing (Daniels et al. 2000). Despite the broad assessments undertaken at the bedside, the problem with this method is that it relies on findings that are subjective and clinician dependent. In recent review, a water test combined with pulse oximetry using coughing, choking, and voice alteration as endpoints is recommended as the most objective method to screen patients with neurological disorders for dysphagia (Bours et al. 2009). Videofluoroscopy (VFS) has traditionally been the gold standard for swallowing assessments (Horner and Massey 1988). It entails the administration of radio-opaque barium liquid and mixed various consistency food with moving images captured in the lateral and anteroposterior views (Fig. 5.1a). The real-time video radiographic image provides visualization of the structures, movement, and coordination of swallowing. Abnormal oropharyngeal and esophageal anatomy can be readily identified. VFS allows an in-depth examination of the cause of aspiration and what remedial action, such as modification of posture or food consistency, will help with. Fiberoptic endoscopic evaluation of swallowing (FEES) is an alternative or complementary method to VFS (Langmore et al. 1988). It entails the placement of an endoscope to the level of the uvula or soft palate to give a view of the hypopharynx and larynx (Fig. 5.1b). It permits anatomical assessment as well as sensory testing. Most importantly, it is performed at the bedside with normal meals and can be repeated as often as necessary.

5.2 Neurophysiology Related to rTMS in Post-stroke Dysphagia

A series of experiments from Hamdy et al. probed the role of the motor cortex in dysphagia after stroke using transcranial magnetic stimulation (TMS). Initial studies in healthy volunteers described how midline swallowing muscles are represented bilaterally in the motor cortex but in an asymmetric manner (Hamdy et al. 1996). This has led to the hypothesis that some subjects have a "dominant" swallowing hemisphere.

It was subsequently postulated that stroke affecting the dominant hemisphere was more likely to result in dysphagia (Hamdy et al. 1997). Twenty patients were recruited after their first stroke and eight of the patients were dysphagic. TMS was delivered to sites over both hemispheres in turn, and any resulting electromyographic (EMG)

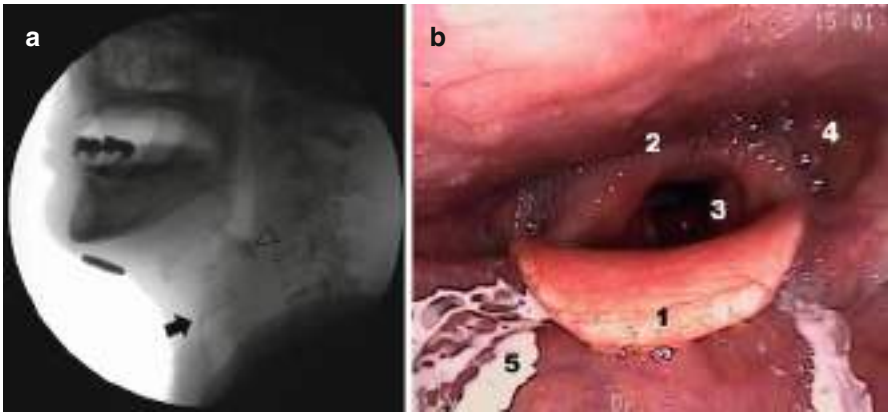

Fig. 5.1 Evaluation tools for swallowing function. (**a**) Videofluoroscopy (VFS). Black arrow shows aspirated barium below the vocal cord and arrowhead shows residue in pyriform sinus. (**b**) Fiberoptic endoscopic evaluation of swallowing (FEES). (1) Epiglottis, (2) esophagus, (3) vocal cord, (4) pyriform sinus, (5) fluid

response at the pharyngeus muscle was recorded. Stimulation of the affected hemisphere produced similarly small EMG responses in both dysphagic and non-dysphagic patients. In contrast, stimulation of the unaffected hemisphere produced significantly smaller responses in the dysphagic patients. Although studied retrospectively, this did indeed suggest that lesions of the dominant hemisphere were more likely to result in dysphagia.

Furthermore, reorganization with increased pharyngeal representation in the non-dominant or unaffected hemisphere appears to be associated with recovery of swallowing function (Hamdy et al. 1998). Twenty-eight post-stroke dysphagic patients were recruited, and their cortical maps in response to TMS of both hemispheres were plotted at 1 week, 1 month, and 3 months after stroke. EMG responses of the thenar muscle were used as a control. The key finding was that dysphagic patients who recovered over time showed an increase in their cortical maps over the unaffected hemisphere at 1 month and 3 months. The patients who remained dysphagic did not show this change in their pharyngeal cortical maps. However, cortical representation of the thenar muscle reappeared in the affected hemisphere.

5.3 Clinical Application of rTMS on Dysphagia After Stroke

Several clinical rTMS studies having the purpose of enhancing the recovery of swallowing function after stroke have been conducted (Table 5.1). The first study was reported in 2009 by Verin et al. (Verin and Leroi 2009). Seven patients with poststroke dysphagia due to hemispheric or subhemispheric stroke for more than 6 months who were diagnosed earlier by videofluoroscopy participated. rTMS at 1 Hz was applied for 20 min per day for 5 days to the healthy hemisphere (focused on mylohyoid muscle) to decrease transcallosal inhibition. Swallowing function was evaluated before

Table 5.1 Summary of the rTMS clinical trials for post-stroke dysphagia treatment

Study (year)	Type of study	Number and type of patients	Onset duration	Target	Control	Stimulation parameters	Evaluations	Results	Side effects
Verin et al. (2009)	A noncontrolled pilot study	Seven patients (3 females, age = 65 ± 10 years) post-stroke dysphagia due to hemispheric or subhemispheric stroke Dx based on VFS	More than 6 months	Contralesional-mylohyoid	None	1 Hz 20 % above the threshold value for 20 min per day every day for 5 days	The dysphagia handicap index and videofluoroscopy (0, 2 weeks)	The score was 43 ± 9 of a possible 120 which decreased to 30 ± 7 ($p < 0.05$) There was an improvement of swallowing coordination, with a decrease in swallow reaction time Aspiration and residue score significantly decreased	No
Khedr et al. (2009)	Randomized controlled study	Twenty-six patients with post-stroke dysphagia due to monohemispheric ischemic stroke, real ($n = 14$) or sham ($n = 12$) Dx based on answers to a swallowing questionnaire, confirmed by bedside examination	Acute (5–10 days after stroke)	Lesional -proximal esophagus	Sham-tilted active coil	10 trains of 3 Hz for 10 min (300 rTMS pulses) at an intensity of 120 % hand motor threshold for five consecutive days	Dysphagia Outcome and Severity Scale, BI, and grip strength were assessed (0, 1, 2 months) The motor-evoked potential (MEP) was assessed (0, 1 month)	Real rTMS led to a significantly greater improvement in dysphagia and motor disability that was maintained over 2 months of follow-up This was accompanied by a significant increase in the amplitude of the oesophageal MEP evoked from either the stroke or non-stroke hemisphere	No

Khedr et al. (2010)	Randomized controlled study	Twenty-two patients with lateral medullary infarction or another brainstem infarction, active ($n=11$) or sham ($n=11$)	Acute	Each, both – proximal esophagus	Sham-tilted active coil	10 trains of 3 Hz for 10 min (300 rTMS pulses) at an intensity of 130 % hand motor threshold for five consecutive days	Dysphagia Outcome and Severity Scale, Barthel Index, NIHSS, and grip strength were assessed (0, 1, 2 months)	Active rTMS improved dysphagia. The LMI group also improved the scores in the Barthel Index All improvements were maintained over 2 months of follow-up	No
Park et al. (2013)	Randomized controlled study	Eighteen patients with unilateral hemispheric stroke oropharyngeal dysphagia, active ($n=9$) or sham ($n=9$) Dx based on VFS	More than 1 month	Contralesional -pharyngeal constrictor	Sham-tilted active coil	10 trains of 5 Hz for 10 min (500 pulses) at intensity of 90 % hand motor threshold for 10 days	Videofluoroscopic dysphagia scale (VDS) and penetration-aspiration scale (PAS) (0, 2 weeks)	VDS and PAS score were decreased	No

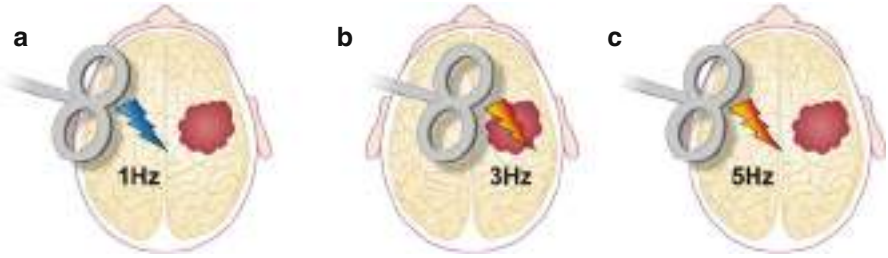

Fig. 5.2 Three different stimulation methods. (**a**) Inhibitory stimulation on contralesional intact motor cortex which makes downregulation of excitability of the motor cortex. (**b**) Excitatory stimulation on ipsilesional affected motor cortex which makes upregulation of excitability of the motor cortex. (**c**) Excitatory stimulation on contralesional intact motor cortex which makes upregulation of excitability of the motor cortex

stimulation and reevaluated 1 week and 3 weeks after the start of rTMS using VFS and dysphagia handicap index. After rTMS, there was an improvement of swallowing coordination, with a decrease in swallow reaction time for liquids and paste and aspiration score significantly decreased for liquids and residue score also decreased for paste. It is meaningful that this was a first attempt to apply rTMS on poststroke dysphagia, but this study was just a small size clinical trial without controls and they did not use pharyngeal constrictors but the mylohyoid as a target.

In the same year, Khedr et al. reported a double-blind randomized controlled rTMS trial (Khedr et al. 2009). Twenty-six patients with poststroke dysphagia due to monohemispheric stroke were randomly allocated to receive real ($n=14$) or sham ($n=12$) rTMS of the affected esophageal cortical area which was taken nearly to be symmetrically opposite the esophagus area of the unaffected hemisphere using a single-pulse motor-evoked potential. Each patient received 10 trains of 3-Hz stimulation at intensity of 120 % hand motor threshold for five consecutive days. Clinical ratings of dysphagia were assessed before and immediately after the last session and then again after 1 and 2 months, and real rTMS led to a significantly greater improvement compared with sham control in dysphagia that was maintained over 2 months of follow-up. Even though they did not use a VFS as an evaluation, it is very meaningful that this study was a randomized controlled trial and they showed long-term follow-up results.

In 2010, same researchers reported another RCT which aimed to compare the effect of active or sham rTMS applied to the motor area of both hemispheres in patients with acute lateral medullary infarction or other brainstem infarctions (Khedr and Abo-Elfetoh 2010). They used same protocol as the above study and the results were also similar.

In recent, Park et al. examined the effects of high-frequency rTMS in the contralesional pharyngeal motor cortex of poststroke dysphagic patients, in a randomized controlled trial (RCT) (Park et al. 2013). Eighteen patients with unilateral hemispheric stroke oropharyngeal dysphagia that lasted more than 1 month were recruited, and real stimulation group received 5 Hz rTMS over contralesional pharyngeal motor cortex for 10 min per day for 2 weeks. The evaluation was performed

using videofluoroscopic dysphagia scale (VDS) and penetration-aspiration scale (PAS) just after treatment cessation and 2 weeks afterward, and rTMS improved the pharyngeal phase of swallow response and reduced the prevalence and severity of penetrations and aspirations immediately and 2 weeks after the treatment.

Conclusion

For many years, dysphagia therapy for stroke patients has been focused on compensatory strategies by using changes in liquid viscosity with thickeners, modifying texture and consistency of solid food, and behavioral strategies (Speyer et al. 2010). These strategies can improve safety of swallowing, but do not change the impaired physiology of swallow biomechanics and do not promote recovery of damaged neural swallow networks in stroke patients. However, in the last decade, new neurostimulation techniques focused on promoting cortical neuroplasticity to recover the swallowing function have been developed.

Some authors sought to restore the pharyngeal cortex functionality of the affected hemisphere by inhibiting the intact hemisphere to decrease transcallosal inhibition or by stimulating the affected hemisphere. These strategies are a commonly used paradigm in the rehabilitation of different stroke-related disorders (such as extremities) with unilateral hemisphere representation. However, Park et al. used a different strategy that aimed at increasing the excitability of the contralesional healthy pharyngeal motor cortex, promoting a similar reorganization of neural connections as that observed during the spontaneous recovery of the swallow function after stroke based on Hamdy's studies (Hamdy et al. (1996, 1997, 1998). Therefore, there exist three different kinds of stimulation ways to provoke swallowing recovery after unilateral hemispheric stroke (Fig. 5.2). No one can say which method is better than the others till further studies are conducted that compare the effects of these approaches. However, we must know that as the swallow system is bilaterally innervated and has different neuroplastic behavior than unilateral systems, the application of inappropriate therapeutic paradigms could even lead to maladaptive plasticity that may interfere with swallowing recovery (Rofes et al. 2013).

Of course, it is true that the exact number of the studies related to this new technique is too small to determine the rTMS treatment guideline for dysphagia after stroke. Given the variability of methods used and of the paucity of trials, "no recommendation" (Andrews et al. 2013; Guyatt et al. 2008) can be given in favor of rTMS therapy for dysphagia after stroke in routine clinical practice. More well-designed studies will be necessary in the near future.

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Basic Principles of rTMS in Aphasia Treatment After Stroke

6

Wolf-Dieter Heiss and Alexander Thiel

Abstract

Aphasia, the most disabling functional defect after ischemic stroke, affects more than a third of all stroke victims. It improves during the first 4 weeks in one-third of patients and during the first 6 months in approximately half of them. Early and intensive speech and language therapy (SLT) is the only effective treatment to date but usually is limited in duration and intensity. Therefore, improved and additional treatment strategies are required to improve recovery of language functions.

Poststroke aphasia results from the lesion of cortical areas involved in the motor production of speech (Broca's aphasia) or in the semantic aspects of language comprehension (Wernicke's aphasia). Such lesions induce an important reorganization of speech/language-specific brain networks due to an imbalance between cortical facilitation and inhibition. In fact, functional recovery is associated with changes in the excitability of the damaged neural structures and their connections. Two main mechanisms are involved in poststroke recovery: the recruitment of perilesional regions of the left hemisphere in case of small lesions and the acquisition of language processing ability in homotopic areas of the nondominant right hemisphere when left hemispheric language abilities are severely impaired.

The purpose of NIBS application in the neurorehabilitation of aphasic patients is to act on specific networks involved in the pathophysiology of language processing and to promote adaptative cortical reorganization after stroke. The rehabilitation of poststroke aphasia refers to two different strategies: the recruitment of perilesional cortical regions in the dominant (left) hemisphere on one hand and the development of language ability in the nondominant (right) hemisphere on the other hand using either rTMS or tDCS. The compensatory potential of the nondominant hemisphere is probably limited, and the recovery from poststroke

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aphasia seems to be more effective in patients who recover left hemisphere networks and left IFG function.

Therefore, the majority of NIBS trials in poststroke aphasia aimed to reinforce the activity of brain regions in the left hemisphere. This goal can be achieved by using an excitatory NIBS protocol (either high frequency rTMS, intermittent TBS (iTBS) or anodal tDCS) to reactivate the lesioned area or an inhibitory NIBS protocol (either low-frequency rTMS or cathodal tDCS) to reduce activities in the contralesional homologous area.

Most conventional rTMS studies employed an inhibitory paradigm (low-frequency stimulation) for the stimulation of the contralesional right IFG (pars triangularis, BA 45) aiming to reduce right hemisphere hyperactivity and transcallosal inhibition exerted on the left Broca's area. In our controlled proof-of-principle study, 30 patients with subacute poststroke aphasia were randomized to a 10-day protocol of 20 min inhibitory 1 Hz rTMS over the right triangular part of the posterior inferior frontal gyrus (pIFG) or sham stimulation followed by 45 min of speech and language therapy (SLT). Activity in language networks was measured with O-15-water positron emission tomography during verb generation before and after treatment. Language performance was assessed using the Aachen Aphasia Test battery (AAT). The results of this study indicate that inhibitory 1Hz rTMS over the right pIFG in combination with SLT improves recovery from poststroke aphasia and favors recruitment of left hemisphere language networks.

6.1 Introduction

With an incidence of ≈200/100,000 population per year, stroke is the second leading cause of mortality and the most frequent cause of disability presenting a great burden to society and causing huge expenses for health care systems. In approximately 30 % of stroke victims the impairment or loss of language function – aphasia – is the leading deficit, which improves within 6 months in approximately half of them (Pedersen et al. 1995; Engelter et al. 2006; Inatomi et al. 2008). The disability in daily life due to poststroke aphasia (PSA) is dependent on the subtype of stroke and its location, which determines the type of language disturbance affecting receptive or expressive functions or both (Ferro et al. 1999; Croquelois and Bogousslavsky 2011; Gialanella 2011). Speech and language therapy is able to improve various aspects of aphasia, namely, functional communication as well as expressive and receptive performance (review in Brady MC et al. (2012)) especially when started early in the poststroke phase and continued with 5–10 h a week for an extended period of time (Robey 1998). The effect of SLT might be improved by additional therapeutic strategies such as noninvasive brain stimulation (NIBS), which act on the excitability and plasticity of cortical regions (reviews in Hamilton et al. (2011), Schlaug et al. (2011), Naeser et al. (2010, 2012), Mylius et al. (2012b), Mally (2013), Shah et al. (2013)) and thereby increase the ability to recruit additional non-used parts of the functional network.

6.2 Role of Functional Imaging in Stroke Patients

The functional deficit after a focal brain lesion is determined by the localization and the extent of the tissue damage; recovery depends on the adaptive plasticity of the undamaged brain, especially the cerebral cortex, and of the non-affected elements of the functional network. Since destroyed tissue usually cannot be replaced in the adult human brain, improvement or recovery of neurological deficits can be achieved only by reactivation of functionally disturbed but morphologically preserved areas or by recruitment of alternative pathways within the functional network. This activation of alternative pathways may be accompanied by the development of different strategies to deal with the new functional-anatomical situation at the behavioral level. Additionally, the sprouting of fibers from surviving neurons and the formation of new synapses could play a role in long-term recovery. These compensatory mechanisms are expressed in altered patterns of blood flow or metabolism at rest and during activation within the functional network involved in a special task, and therefore functional imaging tools can be applied successfully for studying physiological correlates of plasticity and recovery noninvasively after localized brain damage. The observed patterns depend on the site, the extent, and also the type and the dynamics of the development of the lesion; they change over time and thereby are related to the course and the recovery of a deficit. The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

For the analysis of the relationship between disturbed function and altered brain activity, studies can be designed in several ways: measurement at rest, comparing location and extent to deficit and outcome (eventually with follow-up); measurement during activation tasks, comparing changes in activation patterns to functional performance; and measurement at rest and during activation tasks early and later in the course of disease (e.g., after stroke) to demonstrate recruiting and compensatory mechanisms in the functional network responsible for complete or partial recovery of disturbed functions. Only a few studies have been performed applying this last and most complete design together with extensive testing for the evaluation of the quality of performance finally achieved.

A large amount of data has been collected over the past years with functional imaging of changes in activation patterns related to recovery of disturbed function after stroke (Herholz and Heiss 2000; Rijntjes and Weiller 2002; Thirumala et al. 2002; Rossini et al. 2003; Ward 2007; Cramer 2008; Eliassen et al. 2008).

6.2.1 The Principle of Functional and Activation Studies Using Positron Emission Tomography (PET)

The energy demand of the brain is very high and relies almost entirely on the oxidative metabolism of glucose. Mapping of neuronal activity in the brain can be primarily achieved by quantitation of the regional cerebral metabolic rate for glucose

(rCMRGlc), as introduced for autoradiographic experimental studies by Sokoloff et al. (1977) and adapted for positron emission tomography (PET) in humans by Reivich et al. (1979). The cerebral metabolic rate for glucose (CMRGlc) can be quantified with PET using 2-[^{18}F]fluoro-2-deoxyglucose (FDG) and a modification of the three-compartment model equation developed for autoradiography by Sokoloff et al. (1977). Because of its robustness with regard to procedure and model assumptions, the FDG method has been employed in many PET studies, including prediction of recovery after stroke (Heiss et al. 1993).

Almost all commonly applied methods for the quantitative imaging of CBF are based on the principle of diffusible tracer exchange. Using ^{15}O-labeled water administered either directly by intravenous bolus injection or by the inhalation of ^{15}O-labeled carbon dioxide, which is converted into water by carbonic anhydrase in the lungs, CBF can be estimated from steady-state distribution or from the radioactivity concentration-time curves in arterial plasma and brain. Typical measuring times range between 40 s and 2 min, and because of the short biological half-life of the radiotracers, repeat studies can be performed (Frackowiak et al. 1980; Herscovitch et al. 1983).

Functional activation studies as they are used now rely primarily on the hemodynamic response, assuming a close association between energy metabolism and blood flow. The regional values of CBF or CMRGlc represent the brain activity due to a specific state, task, or stimulus in comparison to the resting condition, and color-coded maps can be analyzed or correlated to morphological images. Due to the radioactivity of the necessary tracers, activation studies with PET are limited to a maximum of 12 doses of ^{15}O labeled tracers, e.g., 12 flow scans, or two doses of ^{18}F-labeled tracers, e.g., two metabolic scans. Especially for studies of glucose consumption, the time to metabolic equilibrium (20–40 min) must be taken into consideration, as well as the time interval between measurements required for isotope decay (HT for ^{18}F 108 min, for ^{15}O 2 min).

Regional CMRGlc and regional CBF can be measured quantitatively by PET. State-of-the-art PET scanners are equipped with thousands of detectors arranged in up to 24 rings, simultaneously scanning 47 slices of <5 mm thickness. Pseudocolor-coded tomographic images of the radioactivity distribution are then reconstructed from the many projected coincidence counts by a computer, using CT-like algorithms and reliable scatter and attenuation corrections. Typical in-plane resolution (full width at half-maximum) is <5 mm; 3D data accumulation and reconstruction permit imaging of the brain in any selected plane or view.

6.2.2 Poststroke Aphasia

Studies of glucose metabolism in aphasia after stroke have shown metabolic disturbances in the ipsilateral hemisphere caused by the lesion and in the contralateral hemisphere caused by functional deactivation (diaschisis) (review in Heiss et al. (2003)). In right-handed individuals with language dominance in the left hemisphere, the left temporoparietal region, in particular the angular gyrus, supramarginal gyrus, and lateral and transverse superior temporal gyrus are the most

frequently and consistently impaired, and the degree of impairment is related to the severity of aphasia. The functional disturbance as measured by rCMRGlc in speech-relevant brain regions early after stroke is predictive of the eventual outcome of aphasia, but also the metabolism in the hemisphere outside the infarct was significantly related to outcome of poststroke aphasia, a finding supporting previous results of a significant correlation of CMRGlu outside the infarct with functional recovery (Heiss et al. 1993). Additionally, the functionality of the bihemispheric network has a significant impact on outcome: although the brain recruits right hemispheric regions for speech processing when the left hemispheric centers are impaired, Outcome studies reveal that this strategy is significantly less effective than repair of the speech-relevant network in adults. That the quality of recovery is mainly dependent on undamaged portions of the language network in the left hemisphere and to a lesser extent on homologous right hemisphere areas can be deduced from activation studies in the course after poststroke aphasia (Heiss et al. 1999). The differences in improvement of speech deficits were reflected in different patterns of activation in the course after stroke: the subcortical and frontal groups improved substantially and activated the right inferior frontal gyrus and the right superior temporal gyrus (STG) at baseline and regained regional left STG activation at follow-up. The temporal group improved only in word comprehension; it activated the left Broca's area and supplementary motor areas at baseline and the precentral gyrus bilaterally as well as the right STG at follow-up, but could not reactivate the left STG. These results were confirmed in comparable studies (Cao et al. 1999; Warburton et al. 1999; Saur et al. 2006).

6.2.2.1 Combination of Repetitive Transcranial Magnetic Stimulation (rTMS) with Activated Imaging

rTMS is a noninvasive procedure to create electric currents in discrete brain areas which, depending on frequency, intensity, and duration, can lead to transient increases and decreases in excitability of the affected cortex. Low frequencies of rTMS (below 5 Hz) can suppress excitability of the cortex, while higher-frequency stimulation (5–20 Hz) leads to an increase in cortical excitability (Kobayashi and Pascual-Leone 2003). Collateral ipsilateral as well as transcallosal contralateral inhibition can be demonstrated by simultaneous rTMS and PET activation studies (Thiel et al. 2006): at rest, inhibitory low-frequency (1 Hz) rTMS decreased blood flow ipsilaterally and contralaterally. During verb generation, rCBF was decreased during rTMS ipsilaterally under the coil but increased ipsilaterally outside the coil and in the contralateral homologous area. The effect of rTMS was accompanied by a prolongation of reaction time latencies to verbal stimuli.

Increases in relative cerebral perfusion in contralateral homologous language regions during speech in chronic aphasic patients indicated overactivation of right language homologues. This right hemisphere overactivation may represent a maladaptive strategy and can be interpreted as a result of decreased transcallosal inhibition due to damage of the specialized and lateralized speech areas. The role of activation in the right hemisphere for residual language performance can be investigated by combining rTMS with functional imaging, e.g., PET. In patients in whom

verb generation activated predominantly the right inferior frontal gyrus, this response could be blocked by inhibitory low-frequency (1 Hz) rTMS over this region. These patients had lower performance in verbal fluency tasks than patients with effects of rTMS only over the left IFG, suggesting a less effective compensatory potential of right-sided network areas.

Activation studies in the course of recovery of poststroke aphasia suggest various mechanisms for the compensation of the lesion within the functional network. Despite differences among the activation and stimulation paradigms and the heterogeneity of patients included in different imaging studies, a hierarchy for effective recovery might be deduced:

- Best, even complete, recovery can only be achieved by restoration of the original activation pattern after small brain damage outside primary centers.
- If primary functional centers are damaged, reduction of collateral inhibition leads to activation of areas around the lesion (intrahemispheric compensation).
- If the ipsilateral network is severely damaged, reduction of transcallosal inhibition causes activation of contralateral homotopic areas, which is usually not as efficient as intrahemispheric compensation. In some patients with slowly developing brain damage, the language function can be completely shifted to the right hemisphere.

In most instances, the disinhibition of homotopic areas contralateral to the lesion impairs the capacity for recovery – a mechanism, which might be counteracted by inhibitory low-frequency (1 Hz) rTMS of these contralateral active areas. This approach might open a new therapeutic strategy for poststroke aphasia.

6.3 Effect of NIBS on Recovery of Poststroke Aphasia

Noninvasive brain stimulation (NIBS) can modulate the excitability and activity of targeted cortical regions and thereby alter the interaction within pathologically affected functional networks; this kind of intervention might promote the adaptive cortical reorganization of the language network after stroke (Winhuisen et al. 2005; Martin et al. 2009; Hamilton et al. 2011; Schlaug et al. 2011; Mylius et al. 2012a). Since recovery from poststroke aphasia seems to be more effective in patients who recover function in the left inferior frontal gyrus, NIBS trials aimed to activate this region: this effect can be achieved by excitatory NIBS (high-frequency repetitive transcranial magnetic stimulation, rTMS; intermittent theta-burst stimulation, iTBS; anodal transcranial direct current stimulation, tDCS) to reactivate the perilesional area or by inhibitory NIBS (low-frequency rTMS or cathodal tDCS) to reduce increased activities in the contralesional homologous areas (review in Mylius et al. (2012a), (Shah et al. 2013)).

Most NIBS studies in poststroke aphasia employed inhibitory low-frequency rTMS for stimulation of the contralesional pars triangularis of the right inferior frontal gyrus (BA 45) in order to reduce right hemisphere hyperactivity and transcallosal inhibition on the left Broca's area (Naeser et al. 2011). In single case studies or small

case series with chronic poststroke aphasia, a beneficial effect on speech performance lasting for several months was observed without any control condition (reviewed in Naeser et al. (2012)). One controlled study (Barwood et al. 2011) in a small series of 12 patients in the chronic stage used placebo stimulation with a sham coil in a parallel group design and showed improved performance in picture naming accuracy and latency. In one study combining rTMS with intensive speech therapy (Abo et al. 2012), the site of stimulation was selected by fMRI, and improvements were observed for comprehension and repetition in nonfluent aphasics and for spontaneous speech in fluent aphasics. This study only included chronic cases; comparison to a control group is missing. A controlled study in 40 poststroke aphasics in the subacute stage only showed a slight difference between the group treated with rTMS in combination with SLT and the control group receiving sham rTMS before SLT (Seniow et al. 2013); only a few severely aphasic rTMS patients improved considerably. This weak effect might be related to rTMS applied not selectively to the right pars triangularis, since MRI-guided neuronavigation was not used to define the region of stimulation. A controlled trial with inhibitory cathodal tDCS stimulation of the nondominant right Wernicke's area in patients with subacute global aphasia resulted in some improvement of comprehension in the treatment group (You et al. 2011).

Several studies attempted to restore perilesional neuronal activity in the injured left inferior frontal gyrus by applying excitatory high-frequency rTMS or iTBS or anodal tDCS to small series of patients in the chronic stage after stroke. They showed favorable effects in speech performance for several weeks to a few months (reviews in Holland and Crinion (2012, Mylius et al. 2012a)). Only one study coupled ipsilesional anodal tDCS to language therapy in chronic nonfluent aphasia and observed improved speech/language performance for 1 week to 2 months (Baker et al. 2010).

In a sham-controlled study, Khedr et al. (2014) introduced a dual-hemisphere rTMS study design, aiming at simultaneously reducing activation of the rIFG by inhibitory rTMS and strengthening the left hemisphere language network by excitatory high-frequency stimulation over the left IFG followed by SLT in patients with subacute aphasia poststroke. Participants receiving real stimulation showed significantly greater improvements in linguistic performance of the hemispheric stroke scale language section compared to sham-treated persons directly after treatment and in a 1- and 2-month follow-up. This promising approach might be particularly beneficial for patients with enough spared brain tissue in the left IFG, but bilateral rTMS might require further safety precautions, e.g., monitoring by electroencephalography to avoid undesirable side effects like seizures.

6.3.1 Proof-of-Principle: Reversal of Right Hemispheric Activation by rTMS and Improvement of Poststroke Aphasia

In a randomized controlled study, the effect of inhibitory rTMS on pars triangularis of the right inferior frontal gyrus (IFG) in comparison to rTMS vertex stimulation in combination to speech and language therapy (SLT) on the pattern of brain

activation and on recovery of poststroke aphasia in the subacute stage was investigated. Twenty-nine right-handed patients with left hemispheric infarcts were included, 15 received right inferior frontal gyrus stimulation, and 14 were sham stimulated over the vertex and served as controls (Thiel et al. 2013; Heiss et al. 2013). Change in global AAT test scores between initial and follow-up assessment was significantly higher ($P = 0.002$, t-test for independent samples) in rTMS-treated right-handed patients (22.4 ± 11.77) than in sham-treated patients (8.6 ± 10.06) (Fig. 6.1a). There was no significant interaction between treatment effect and AAT subtests indicating that all subtests contribute equally to the observed treatment effect, with the largest difference in picture naming performance (6.1 ± 3.35).

During verb stimulation before initiation of treatment, all patients showed an abnormal activation pattern involving large parts of the language network in the nondominant right hemisphere (Fig. 6.2).In right-handed patients who received real rTMS over the contralesional IFG before each SLT session, a shift of activation to the ipsilateral dominant hemisphere was observed, and the change in the activation volume (AV) indices (AVI calculated from: AV ipsilat – AV contralat divided by AV ipsilat + AV contralat) was significantly larger (36.6 ±31.55) than in sham-stimulated patients (−7.6 ± 45.42), $P = 0.006$, paired t-test), thus indicating a larger shift of network activity toward the left, ipsilesional hemisphere (Fig. 6.1b). There was a significant interaction between treatment effect and AVI before and after treatment ($P = 0.023$) (Fig. 6.1c). There was no difference in AVI within the sham group between the two time points and between the sham and tms group prior to treatment. However, AVI was significantly higher in the rTMS group after treatment when compared to pretreatment ($P = 0.001$) and to sham group (Fig. 6.2b).

In our study PET could be applied during NIBS to demonstrate the immediate modulation of network activity as well as longer-lasting alterations related to recovery, thus lending direct support to the hypothesis of the relationship between activation shift and improvement of subacute poststroke aphasia. The results of this randomized controlled trial with rTMS of the contralesional homotopic IFG indicate that NIBS is more efficient than sham treatment in right-handed patients in the subacute stage after stroke. Although only one stimulation site was tested in different types of aphasia, the intervention group experienced a significantly larger improvement in the global AAT score than the sham group. Our study demonstrated again the change in activation pattern in all patients and the rTMS effect, which is based on the inhibition of overactivation in homotopic speech areas of the contralesional hemisphere. As a proof of principle, the shift of activation back to the dominant hemisphere was associated with significant improvement of the language function in the group treated with rTMS combined with SLT. However, in the sham-treated group, the activation in the contralesional hemisphere usually became more accentuated, despite this group showing some improvement of language function after SLT.

As a consequence, determination of altered activation patterns in poststroke aphasia by fMRI or PET might help to select the best stimulation site – e.g., the contralateral homotopic Broca's or Wernicke's area (Abo et al. 2012) – and will be of importance in patients with altered speech dominance. Two populations that may exhibit altered speech dominance are left-handed and right-handed patients with

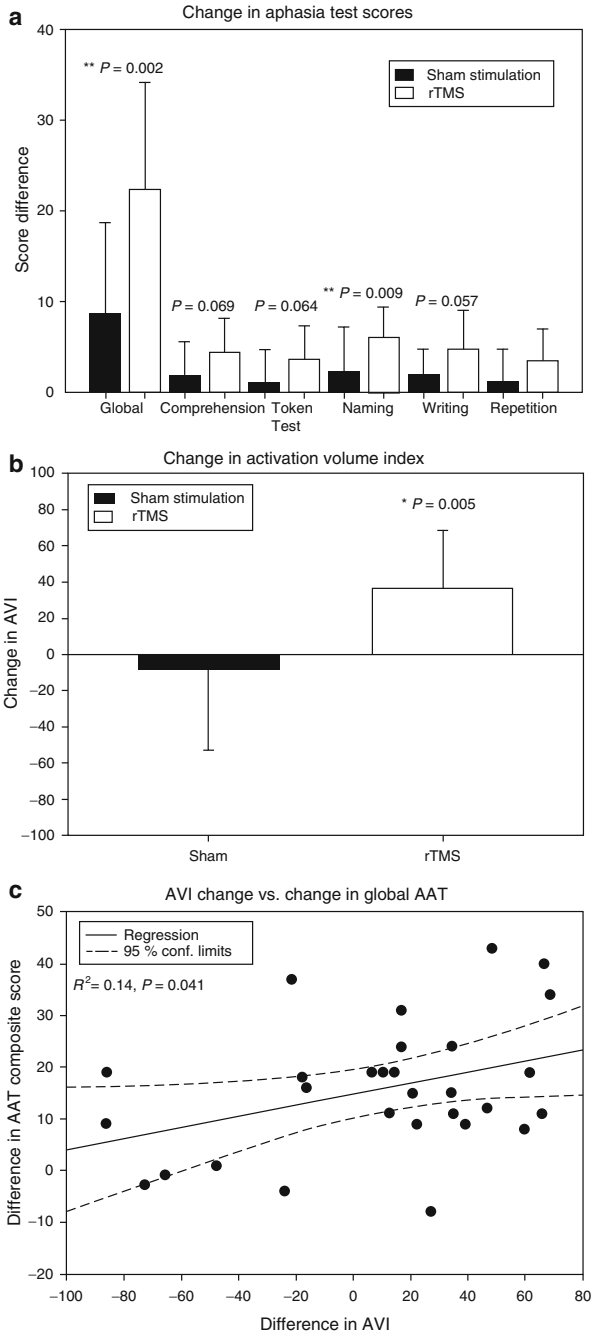

Fig. 6.1 (**a**) (Aphasia score) Change in aphasia test scores pre and post sham or rTMS treatment. There is a significant larger change in global aphasia scores for the TMS group. In the AAT subtest, a significantly larger change for the TMS group was observed in picture naming and trends in the subtests comprehension, token test, and writing. No difference was observed for word repetition. (**b**) (AVI) The activation volume index is a measure of task associated activated brain volume with positive values indicating larger activated networks in the left hemisphere. The graph shows the treatment-associated changes in AVI. In the TMS group, larger networks are recruited in the left hemisphere after the treatment (positive change in AVI indicates left-ward shift), whereas no such shift of network activity to the left hemisphere occurs in sham-treated subjects. (**c**) (Correlation) Significant linear relationship between left-ward shift in network activity (AVI) and change in global aphasia test score

so-called crossed aphasia. In both left- and right-handed subjects, language dominance is thought to be distributed along a continuum from pure left over relative bilateral to predominantly right-sided dominance based on functional imaging and

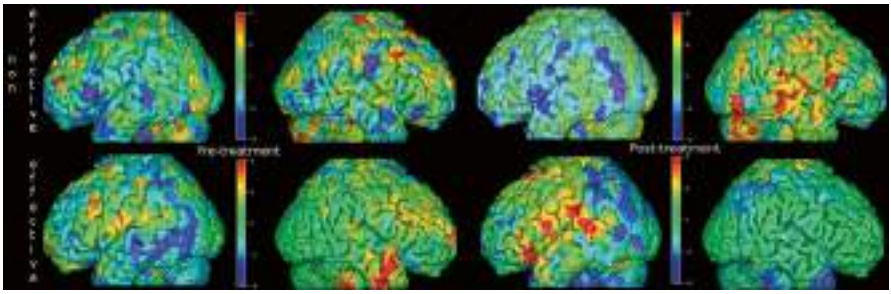

Fig. 6.2 (Effect shift) Language activation PET scans of a sham-treated subject (*top row*) show bilateral activity pretreatment, which consolidates in the right hemisphere after treatment (non-effective shift). In a TMS-treated subject (*bottom row*), the initially bilateral activity shifts to the left hemisphere posttreatment (effective shift)

evoked flow transcranial Doppler studies (Knecht et al. 2000). While a right-ward dominance pattern is rare in right-handers, it is more frequently observed in left-handers. It has also been shown that the extent of right-sided dominance (independent of handedness) predicts the efficacy of rTMS applied to the left hemisphere to interfere with language processing (Knecht et al. 2002). The exact localization of language functions in right hemispheric aphasia could be determined in selected cases by PET of glucose metabolism (Cappa et al. 1993), by direct cortical stimulation (Oishi et al. 2006), or by fMRI (Vandervliet et al. 2008). However, contrary to right-handers, TMS did not achieve a significant shift of network activity back to the ipsilesional hemisphere in two left-handed patients with right hemispheric dominance (Heiss et al. 2013). This finding might point against the hypothesis that the situation in left-handed aphasics is a simple reversal of the mechanisms in right-handers and that recovery might depend much more on the preexisting bilateral network organization than in right-handers. This preliminary observation indicates that a patient's susceptibility to develop aphasia after stroke is strongly related to the preexisting dominance pattern. To what extent the recovery from aphasia is related to this is unknown. In these cases identification of the activation pattern in post-stroke aphasia might give hints for the changes in the functional network and for eventually effective modifications by NIBS.

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Therapeutic Applications of rTMS for Aphasia After Stroke

7

Priyanka P. Shah-Basak and Roy H. Hamilton

Abstract

Repetitive transcranial magnetic stimulation is a powerful treatment tool for aphasia because it can directly leverage our understanding of neural basis of language disorders and provide a novel and promising treatment. The reorganization in the neural representation of language functions after an aphasia-causing stroke critically underpins spontaneous language recovery. The course of this reorganization is largely shaped by the extent of damage and the duration since stroke onset. The therapeutic applications of rTMS in poststroke aphasia have capitalized on a growing but incomplete understanding of these neural changes, in order to guide the location and type of stimulation. Converging evidence from a variety of treatment studies suggests that rTMS can significantly augment performance of a number of language functions. However, evidence also suggests that aphasic patients exhibit significant variability in clinical characteristics and in turn in their response to rTMS treatment. In this chapter, we provide a review and a critical appraisal of published rTMS treatment studies in patients with aphasia (PWA). Based on this evidence, we conclude that rTMS can be effective in reducing symptoms of aphasia. However, because of a great deal of heterogeneity in rTMS methodologies, we recommend standardization and further investigation of rTMS in a context of large-scale clinical randomized trials. These trials should take an individualized treatment approach that is informed by mechanism(s) of recovery on a patient-by-patient basis rather an one-size-fits-all approach.

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7.1 Introduction

The central aim of clinical neurorehabilitation is to facilitate the recovery of function after nervous system injury. Insofar as the regeneration of neural structures in adult humans is limited, one of the principal mechanisms by which functional recovery occurs is via processes that fall under the broad heading of neuroplasticity. Neuroplastic processes refer to those changes in neural pathways and synapses that result from alterations in behavior, modification of the extrinsic or intrinsic environment, or injury (Cramer et al. 2011). One important category of change that occurs in the setting of focal brain injury is the modification of large networks of neurons that represent specific cognitive operations, particularly those operations that had previously been represented by areas that have been injured or destroyed. This kind of functional remapping is highly germane to recovery from aphasia after stroke. Aphasia—the loss of language function—is a common and often devastating consequence of stroke that arises from infarction of perisylvian structures in the language-dominant (typically left) hemisphere (Berthier 2005). As we will discuss in detail in this chapter, the brains of patients who experience aphasia after stroke undergo a variety of complex changes in function involving both perilesional left hemisphere areas and the uninjured right hemisphere. Some of these changes appear to be compensatory and beneficial in nature, while others may be extraneous or even deleterious.

Transcranial magnetic stimulation (TMS) is a promising and attractive tool in the field of neurorehabilitation of aphasia because it allows for manipulation of brain networks that have reorganized as a result of focal brain injury and can in turn facilitate recovery of language functions (Barker et al. 1985; Walsh and Pascual 2003). As far as its applications in stroke recovery in general—and aphasia treatment specifically—are concerned, mounting evidence suggests that repetitive TMS (rTMS) can have enduring effects on neural activity and network-level connectivity in patient populations (Siebner and Rothwell 2003; Wang et al. 1996). However the application of rTMS to language neurorehabilitation not only requires some understanding of the different types of neuroplastic changes that take place in patients with poststroke aphasia but also the factors that drive these changes to potentially enhance the therapeutic benefits associated with this approach.

In this chapter we will (1a) briefly review several types of changes in the representation of language (henceforth referred to as neuroplastic changes) that are believed to occur spontaneously in the brains of patients who suffer from aphasia due to stroke and (1b) discuss the factors that influence the degree to which these changes impact language performance in different individuals with aphasia. Next, we will (2) provide a critical appraisal of the current status of rTMS treatment approaches that exploit knowledge regarding these neuroplastic changes and lastly (3) provide recommendations in the context of research to strengthen the quality of evidence in future clinical trials using rTMS and to augment recovery in a clinically-relevant and persistent manner.

7.2 Neuroplastic Changes and Factors Influencing These Changes in Poststroke Aphasia

Reorganization in the neural representation of language functions occurs spontaneously (i.e., without any directed interventions) soon after the onset of aphasia after stroke. The neuroplastic changes that subserve this functional reorganization occur not only within the damaged left hemisphere but also in the uninjured right hemisphere. It is generally agreed upon that the recruitment of areas surrounding the damaged left hemisphere is associated with some degree of aphasia recovery (Warburton et al. 1999; Karbe et al. 1998a, b; Ohyama et al. 1996; Cornelissen et al. 2003). However, because the evidence regarding the recruitment of right hemispheric language homologues is mixed, their overall role in recovery remains controversial. While there is evidence suggesting that recruitment of right hemispheric language homologues is beneficial (Thulborn et al. 1999; Musso et al. 1999; Tillema et al. 2008; Basso et al. 1989; Cambier et al. 1983), some researchers argue against their salutary role and instead suggest that activation in these areas is deleterious to recovery (Winhuisen et al. 2005; Thiel et al. 2006; Szaflarski et al. 2013; Postman-Caucheteux et al. 2010).

A frequently invoked theory to explain the deleterious role of the right hemisphere in language is interhemispheric interference, a concept that has been supported in various studies of patients with unilateral motor weakness due to stroke (Naeser et al. 2004; Belin et al. 1996; Rosen et al. 2000a). While the role of right hemispheric homologues remains unresolved, findings from our prior work suggest a middle ground in this debate (Turkeltaub et al. 2011). In this study, it was found that PWA recruited both spared left areas and the right homologues (Ohyama et al. 1996; Basso et al. 1989; Rosen et al. 2000b) and that most right areas contributed meaningfully to the performance of language tasks (Turkeltaub et al. 2011). It was also found, however, that one specific site in the right inferior frontal gyrus (IFG)—the right pars triangularis (PTr; BA45)—was activated during language tasks, but not in a way that suggested that it was contributing positively to performance. This finding suggested that the involvement of right hemispheric areas in language recovery is multidimensional; recruitment of right areas may be largely compensatory with an exception of one or more noisy sites (such as PTr), which may impede rather than aid meaningful reorganization in language networks (Turkeltaub et al. 2011).

Based on this assembled evidence, Hamilton and colleagues (2011) outlined three theoretical models of recovery-inducing neuroplastic changes (Hamilton et al. 2011) that are highly relevant to our discussion of the therapeutic applications of rTMS in the subsequent sections. These theorized changes include the (1) recruitment of residual and perilesional language areas in the damaged left hemisphere (Warburton et al. 1999; Karbe et al. 1998a, b; Ohyama et al. 1996; Cornelissen et al. 2003), (2) compensatory recruitment of homotopic language areas in the right hemisphere (Thulborn et al. 1999; Musso et al. 1999; Tillema et al. 2008), and (3) inefficient recruitment of a few specific sites (e.g., PTr) in the right hemisphere that hinder recovery (Turkeltaub et al. 2011). As we will discuss in much detail later,

most prior rTMS applications in aphasia can be placed within the framework of one or more of these models of recovery. It is also important to note that neuroplastic changes vary greatly among PWA, as these changes are highly influenced by individual patients' clinical characteristics. Evidence suggests that these characteristics include but are not limited to the extent and location of stroke, the resulting type of language deficits, and the duration since the stroke onset (Naeser et al. 2004; Naeser and Palumbo 1994; Anglade et al. 2014). Individual differences in these clinical factors and their cascading impact on the neuroplastic changes are topics that are also germane to our assessment of the therapeutic applications of rTMS in PWA.

The first of these clinical factors that has been studied in the context of language recovery is size of the stroke. According to the hierarchical model of recovery, recovery from strokes that perturb a small region in the left hemisphere may rely on different neuroplastic mechanisms than large strokes in which critical language areas have been damaged. In small strokes, recovery may rely on the recruitment of residual/perilesional language areas, while in large strokes right hemispheric homologues may be selectively recruited because not many areas in the left hemisphere are spared (Rosen et al. 2000a; Heiss and Thiel 2006). In moderately sized strokes affecting some but not all critical language areas, recovery may be mediated by a combination of events involving intra- and/or interhemispheric processes (Anglade et al. 2014). Aside from the size of lesions leading to aphasia, evidence suggests that the location of injury and the kind of language deficits created by injury—two concepts that are integrally intertwined—can also influence the neuroplastic changes in different patients. One study demonstrated that bilateral activation that was initially found in all PWA transformed into differential patterns of activation depending on the type of manifested language deficits as these patients spontaneously recovered (Thomas et al. 1997). Consistent with this last point, duration of stroke is another key factor that influences the neuroplastic events leading up to recovery in PWA. Because of ongoing neuropathological processes in stroke-affected and neighboring areas (e.g., hypoperfusion, edema, etc.), recovery mechanisms are dynamic and unpredictable in the acute and subacute phases after stroke. However, these mechanisms stabilize in the chronic phase, especially in the absence of further interventions. Evidence indicates that an interhemispheric shift in neural activation patterns takes place from predominately right hemispheric activation observed during the acute phase to activation in the left perilesional/residual areas during both the subacute and the chronic phases (Thulborn et al. 1999; Winhuisen et al. 2005; Saur et al. 2006; Heiss et al. 1999). These shifts in the days, weeks, and months following stroke are strongly associated with improved language abilities (Saur et al. 2006). In addition, these shifts over time from right to left areas suggest that recruitment of right areas (Thiel et al. 2006; Thomas et al. 1997) may be more consistently compensatory during the early (Saur et al. 2006) but not late phases after stroke (Szaflarski et al. 2013).

Evidence presented in this section emphasizes that a closer inspection of differences across patients in their stroke-related damage profiles and resulting language deficits is necessary not only to characterize the bilateral neuroplastic changes associated with spontaneous recovery but also to better inform the therapeutic

applications of rTMS so as to further facilitate recovery. Insofar as most therapeutic applications of rTMS in PWA are informed by these neuroplastic events, it is curious that prior studies have not considered the clinical variability of patients—and the effects of this variability of language recovery mechanisms—as driving factors with respect to treatment-related effects. Despite findings in these studies that suggest that PWA may benefit from one specific rTMS approach, we argue in subsequent sections that an individualized approach that meets each patient's needs may be more efficacious.

7.3 Therapeutic Applications of rTMS in Aphasia

Treatment studies involving rTMS in poststroke aphasia have largely been informed by one or more of the mechanistic principles of neuroplastic change that mediate recovery. However, despite the fact that a core set of principles motivate the approach taken by investigators, there has been a great deal of variability in approach across studies, in particular with respect to the (1) selection of outcome measures to index improvement in language functions, (2) specific rTMS parameters and protocols, and (3) the clinical characteristics of patients included in these studies.

In this section, we will discuss these different aspects to systematically characterize the heterogeneity between studies before we examine the evidence surrounding the therapeutic use of rTMS in PWA. We will critically appraise the methodological quality of a selected group of rTMS treatment studies and discuss the rTMS approaches applied in these specific studies in greater detail. Next, we will summarize the evidence and use the binary GRADE system (Guyatt et al. 2008) to determine the strength of our recommendation (weak or strong) in favor of large-scale, clinical applications of rTMS in treating PWA. Lastly, we will list a few important guidelines for planning future clinical trials, which will serve to address shortcomings that we have identified in this literature and to strengthen the evidence further so as to advance the applications of rTMS in clinical settings.

7.3.1 Heterogeneity in Study Methodology

7.3.1.1 Selection of Outcome Measures

To assess the therapeutic benefits of rTMS, most studies have applied neuropsychological language measures, of which the most commonly used have been picture-naming tasks—tasks requiring patients to articulate the names of objects typically displayed as line drawings. Since most PWA have difficulties in confrontational naming (DeLeon et al. 2007), an increase in the number of items named (accuracy) and/or a decrease in time taken to respond to these items (reaction time) (Snodgrass and Vanderwart 1980; Bates et al. 2003) has been interpreted as being reflective of improvement in at least one aspect of language ability. Neuropsychological batteries that index the overall aphasia severity, or changes in severity, have also been widely used in rTMS treatment studies; commonly used batteries include the Boston

Diagnostic Aphasia Examination (BDAE), the Aachen Aphasia Test (AAT), the Western Aphasia Battery (WAB), and the Aphasia Severity Rating Scale (ASRS).

Significant improvement following rTMS treatment in naming accuracy (e.g., Abo et al. 2012; Thiel et al. 2013a; Barwood et al. 2013) and latency (e.g., Kindler et al. 2012; Barwood et al. 2012), as well as in auditory comprehension (e.g., Barwood et al. 2011a; Kakuda et al. 2011), spontaneous speech and fluency (e.g., Abo et al. 2012; Medina et al. 2012; Szaflarski et al. 2011; Waldowski et al. 2012), and word repetition (e.g., Abo et al. 2012; Kakuda et al. 2011), has been reported after daily sessions of rTMS. In a handful of studies, amelioration in overall aphasia severity has also been reported (Thiel et al. 2013a; Waldowski et al. 2012; Khedr et al. 2014). This assembled evidence strongly suggests a favorable role of rTMS in improving a variety of language functions in PWA, though measures used to monitor improvement have varied widely across studies. One important caveat to take note of is that because of the differences in outcome measures, as well as in the applied rTMS protocols (discussed in the next section), it is difficult to comment on the relative benefits of one rTMS protocol over the other. In addition, because very few studies included an ecological language measure, it is unclear whether the improved performance on these neuropsychological batteries would transfer to functionally relevant benefits such as improving patients' everyday communication abilities.

7.3.1.2 RTMS Protocols and Localizing Targets for Stimulation

Consistent with models suggesting either a maladaptive role of right hemispheric homotopic areas or of a few noisy sites within the right hemisphere, most rTMS treatment studies have administered low-frequency or inhibitory rTMS (1–4 Hz) targeting specific areas within the right frontotemporal network. Thus far, one of the most frequently stimulated targets in this network (Fig. 7.1) is the right inferior frontal gyrus (IFG). Other studies have targeted right superior temporal areas (Abo et al. 2012; Barwood et al. 2011b, c, 2013; Kindler et al. 2012; Kakuda et al. 2011; Medina et al. 2012; Waldowski et al. 2012; Naeser et al. 2005; Weiduschat et al. 2011; Thiel et al. 2013b). Typically, these areas are stimulated for 20–40 min a day over a course of 10–15 days; for treatment studies that have adopted a specific form of patterned TMS referred to as theta burst stimulation (TBS), the stimulation duration was in the range of 40–200 s. In addition to the common right hemispheric targets, in at least one study (Szaflarski et al. 2011), an excitatory TBS protocol (intermittent TBS; iTBS) was administered to enhance excitability in perilesional left hemisphere areas, based on the notion that left hemispheric perilesional/residual areas play a preferential role in recovery. Furthermore, based on the idea that pairing rTMS with a behavioral language therapy promotes recovery (Karim et al. 2006), most studies have combined the administration of rTMS with 30–60 min of speech and language therapy (Abo et al. 2012; Kakuda et al. 2011; Waldowski et al. 2012; Khedr et al. 2014; Weiduschat et al. 2011; Thiel et al. 2013b). Because patients are required to keep still during rTMS, it is often difficult to provide therapies concurrently with rTMS. Therefore, speech and language therapy in these studies was usually provided in the period immediately following rTMS.

In addition to variability in the anatomic sites of stimulation, researchers have experimented with several different approaches with respect to the kind of rTMS delivered. While most studies employed a single rTMS protocol, Chieffo and colleagues (2014) recently administered both excitatory and inhibitory rTMS to the right inferior frontal language areas (and compared these interventions to sham rTMS) to disentangle the role of these areas in language recovery (Chieffo et al. 2014). This study however was not a treatment study because only a single session of each stimulation type was administered. Their findings suggested that *excitatory* (and not commonly applied inhibitory) stimulation of right homologues can also result in improved language outcomes, which supports theories claiming a compensatory role of these areas to recovery. One other study employed a novel rTMS protocol using two different frequencies within a single rTMS session and demonstrated marked improvement in language performance with this approach (Kakuda et al. 2011; Carey et al. 2010; Iyer et al. 2003); patients were primed with 6 Hz-rTMS for 10 min before the application of low-frequency/1 Hz rTMS for 20 min over the right frontal sites. In another recent study, dual-hemispheric rTMS was delivered in a sequential manner within the same rTMS session. Based on the observation that a bilateral language network is selectively more active during the subacute phase after stroke, first 1 Hz/inhibitory rTMS was applied sequentially over 2 right Broca's homologues (pars triangularis and pars opercularis), which was then followed by 20 Hz/excitatory rTMS over matching regions of the left hemisphere (Khedr et al. 2014). This approach also led to improved language outcomes.

In a few of the rTMS treatment studies in aphasia, the stimulation sites were localized using cranial landmarks and the 10–20 international system (e.g., Kindler

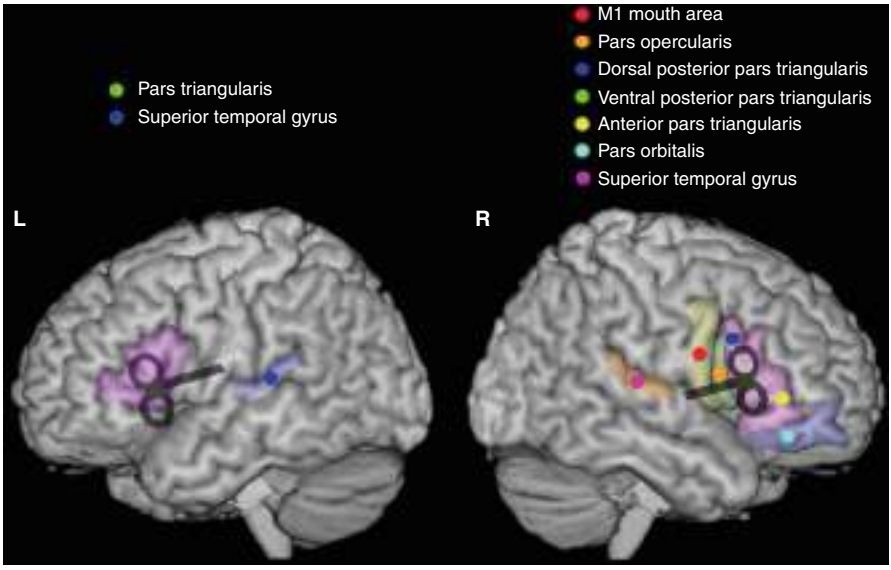

Fig. 7.1 rTMS targets employed in treatment studies of aphasia in the right and left inferior frontal and superior temporal gyri

et al. 2012; Kakuda et al. 2011). However, because this method of localization does not adequately address significant differences in normal neuroanatomy or the large differences in anatomy that can be seen in the setting of stroke, application of rTMS across patients can be highly variable using this approach. Therefore, more recent studies have determined sites of stimulation using frameless stereotactic neuronavigation systems that use individual patients' MRI scans to precisely localize targets for stimulation. This approach minimizes variability across patients and also across multiple sessions of stimulation within subjects (Treister et al. 2013).

Because most treatment studies have been predicated on a specific model of language recovery, a uniform rTMS approach is typically adopted, whereby all patients within a study are stimulated using an identical rTMS protocol. In these studies, as described previously, right PTr within the IFG was most frequently stimulated. Although studies using this approach have reported group-averaged improvements, rTMS applied in this way may not reliably facilitate recovery at the level of individual patients. Correspondingly, to increase the likelihood of therapeutic benefits of rTMS for all patients, there is some effort in this field to establish and validate individualized treatment strategies that use outcome-driven methods for localizing stimulation sites. We (Medina et al. 2012; Hamilton et al. 2010) and our collaborators (Naeser et al. 2011) employed a strategy that involved an optimal site-finding phase as part of the rTMS treatment protocol. In these studies, a single, optimal site was selected on the basis of individual patients' best response to rTMS, which was first applied over several predefined sites, after which protracted rTMS treatment was delivered to the optimal site (Medina et al. 2012; Hamilton et al. 2010; Naeser et al. 2011; Martin et al. 2009). In the site-finding phase, each patient underwent low-frequency rTMS (1 Hz) in six separate sessions during which he or she was stimulated at (Fig. 7.1), the area in the motor cortex corresponding to the mouth, the pars opercularis (POp; BA44), three sites within the PTr (dorsal posterior, ventral posterior, and anterior PTr), and the pars orbitalis (BA47); the Brainsight® Neuronavigation system (Rogue Research, Montreal) was used to precisely depict these sites and also the TMS coil positions over these sites using individual patients' own MRI scans. Optimal response to a site was defined as the site that produced the greatest transient increase in picture-naming accuracy. Subsequently, patients were stimulated at their individually determined optimal site, daily over 10 rTMS (1 Hz) sessions. We found that nine out of ten patients responded optimally after inhibition of the right PTr, while only one patient responded optimally to right pars orbitalis stimulation. Importantly, after protracted rTMS treatment, patients who received real stimulation improved in several measures of language production, while patients who received sham stimulation did not improve on any of the measures. Furthermore, the improvement after real rTMS also persisted over at least 2 months after the treatment ended, suggesting long-term efficacy of this approach (Medina et al. 2012).

While we adopted an approach that employed transient rTMS-induced changes in naming performance as a "functional" localizer for treatment, fMRI-driven approaches are also becoming increasingly popular. Using this approach, optimal sites for stimulation are defined on the basis of activation patterns observed on the

fMRI in response to specific language tasks (Abo et al. 2012; Szaflarski et al. 2011; Allendorfer et al. 2012). For example, in one study, perilesional stimulation targets were determined in each individual patient as areas that exhibited greater activation during a language task (Eaton et al. 2008). Subsequently, intermittent TBS (iTBS) was delivered to these targets in ten daily sessions. After this treatment, significant improvement in semantic verbal fluency was observed and patients tended to report that they were better in their ability to communicate (Szaflarski et al. 2011). Another study extended this work by defining optimal stimulation sites based on both the fMRI activation patterns *and* the type of language deficits exhibited by individual patients (Abo et al. 2012). In patients who were categorized as nonfluent patients, inhibitory rTMS was applied to the areas surrounding the IFG, while in patients with fluent aphasia, rTMS was applied to the superior temporal gyrus (STG; Fig. 7.1). Specific stimulation sites within these territories were then defined by the fMRI activation patterns acquired as the patients performed a language task. In fluent patients, improvement after ten daily 1 Hz rTMS sessions (40 min/day) was reported in auditory and reading comprehension and repetition tasks, and in nonfluent patients, spontaneous speech was reported to have improved.

Because optimal site-finding approaches, whether rTMS- or fMRI-driven, account for individual variability across patients, they are likely an improvement over studies wherein stimulation is guided only by cranial landmarks, although the superiority of one site-finding approach to another is yet to be determined (Heiss and Thiel 2006).

7.3.1.3 Patient Inclusion Criteria and Long-Term Evaluations of rTMS

While most studies have examined the therapeutic effects of rTMS in chronic aphasia, more investigations are emerging that focus on earlier phases of recovery (Kindler et al. 2012; Waldowski et al. 2012; Khedr et al. 2014; Weiduschat et al. 2011; Thiel et al. 2013b). One such study assessed the effects of continuous TBS (cTBS—an inhibitory rTMS protocol) over right Broca's homologue in two separate groups; patients in one group were in the subacute phase of stroke recovery while patients in the other were in the chronic phase (Kindler et al. 2012). Though both patient groups significantly improved after daily sessions of cTBS compared to a sham group, subacute patients were better responders as indicated by marked improvement in timed picture-naming accuracy and reaction time. While this finding favorably supports the application of rTMS in the early phases after stroke, a lack of long-term follow-up after the end of treatment somewhat weakens this claim because it is impossible to disentangle spontaneous recovery from rTMS-induced recovery in this study.

As described earlier, spontaneous recovery is a time-dependent property, whereby neuroplastic changes underlying improved functions are most common and most pronounced in the early phases (acute/subacute) following stroke regardless of treatment (Thiel et al. 2006; Saur et al. 2006). Because spontaneous recovery can easily be misconstrued as rTMS-induced benefits in the acute/subacute phases after stroke, it is paramount to (1) track benefits months beyond the discontinuation of rTMS treatment and (2) demonstrate that these benefits are superior to those seen

in appropriately matched control groups that either receive no treatment or receive sham stimulation. Two recent studies in a relatively large group of subacute patients receiving rTMS tried to address both these concerns. The first of these studies is a randomized, double-blind, sham-controlled study conducted by Waldowski and colleagues (2012; also see Seniow et al. (2013)) who monitored changes in aphasia severity at 15 weeks in a group receiving rTMS compared to the sham group (Waldowski et al. 2012; Seniow et al. 2013). Although a marked reduction in overall aphasia severity was observed after rTMS, improvement in submeasures of language functions such as naming accuracy was not found to be different across groups, with only a slight benefit in reaction time being observed after rTMS. In the second study, Khedr et al. (2014) applied a novel dual-hemispheric, dual-rTMS approach (refer to the previous section for more details) and demonstrated that not only was overall aphasia severity improved after rTMS compared to sham stimulation but also several language submeasures including naming, repetition, fluency, and comprehension (Khedr et al. 2014). Differences in the observed benefits between these studies may have to do with the use of different rTMS protocols, i.e., unilateral versus dual-hemispheric rTMS; however this remains to be confirmed. Nonetheless, these mixed findings emphasize the importance of long-term evaluations, especially in subacute populations, to ascertain rTMS-specific benefits.

Enduring benefits of rTMS have also been reported in several studies of patients in the chronic phase of aphasia recovery (Barwood et al. 2013; Medina et al. 2012). In a chronic patient with nonfluent aphasia, Martin and colleagues (2009) demonstrated improvements in picture-naming accuracy and phrase length after rTMS, which lasted over 3½ years (43 months) (Martin et al. 2009). Recently, Barwood and colleagues (2011a, b, c, and 2013) examined the therapeutic effects of 1 Hz rTMS on right PTr in 12 chronic patients with nonfluent or global aphasia (Barwood et al. 2011a, b, 2013). Both at 2 and 12 months (Barwood et al. 2011b and 2013) after rTMS, 6 patients who received 10 sessions of rTMS improved significantly more (naming, expressive language, and auditory comprehension) than 6 patients who received sham treatment of the same duration.

Overall, more research is warranted to confirm the long-lasting and stimulation-specific therapeutic benefits of rTMS, especially when it is employed early after stroke.

7.3.2 Methodological Quality Ratings: Critical Appraisal of rTMS Treatment Studies in PWA

The number of randomized controlled trials (RCT) examining the therapeutic effects of rTMS in PWA has increased dramatically in the last decade or so. As we continue to learn more about rTMS and its influences on brain functions in patients with stroke, proof-of-concept treatment studies using rTMS have also been implemented. The goal in these studies is not only to demonstrate treatment efficacy but also to examine novel rTMS protocols (Kakuda et al. 2011) or methods of localizing stimulation targets (Abo et al. 2012; Medina et al. 2012) or to test theoretical

models of language and aphasia recovery (Szaflarski et al. 2011). These studies may not be designed as stringently to control for factors such as selection bias or to address external validity to the extent that RCTs are designed to. Therefore, for the purposes of critically appraising the evidence in rTMS treatment studies, we first assessed the methodological quality of both the RCTs and cohort studies (non-RCTs), using the Downs and Black (D&B) tool (1998).

D&B is a 27-item checklist that is validated for both RCT and non-RCTs, and it allows for assessments with respect to different subscales that include quality ratings for (1) *reporting* (is sufficient information provided for readers to make an unbiased judgment about the study findings?), (2) *external validity* (can study findings be generalized to the population from which the sample patients are derived?), (3) *bias* (assesses for measurement bias in the intervention and the outcome), (4) *confounding* (assesses for selection bias), and (5) *power* (assesses whether the study has sufficient power to detect an effect). These subscores provide a profile of methodological strengths and weaknesses of included rTMS treatment studies (Downs and Black 1998), where higher scores indicate higher methodological quality.

Two reviewers rated the 27 items in the D&B quality checklist for treatment studies in which (1) the patients were adults and diagnosed with aphasia due to stroke, (2) the number of patients in the study was ≥4, (3) the outcome measures compared naming abilities before and after brain stimulation, *and* (4) the number of stimulation sessions was ≥3. We excluded studies that were initially published as pilot studies (e.g., Thiel et al. 2013a; Barwood et al. 2011a; Waldowski et al. 2012; Weiduschat et al. 2011) but included updated versions of those studies that were published at a later stage either with more patients (e.g., Seniow et al. 2013; Heiss et al. 2013) or more follow-up evaluations (e.g., Barwood et al. 2013).

While most non-RCTs implemented a pre-post or within-subject design in which all patients underwent treatment with rTMS without a separate control group, a few were crossover study designs wherein same patients underwent both the real and sham treatments with the order of real and sham conditions counterbalanced across patients. D&B subscores for included studies are provided in Table 7.1 and are separated by study designs. Not surprisingly, studies with a within-subject design had the lowest overall methodological rating with the mean score of 19.7. These studies specifically scored low on the internal validity measures (bias, 3.7 out of 7; confounding, 1.7 out of 6) perhaps because of a possibility of uncontrolled and repeated testing effects. Notably, within-subject designs were invariably implemented in PWA who were in the chronic phase of recovery, whereas RCTs were more frequently implemented in subacute populations (except Barwood et al. 2013). Arguably, most of these within-subject designs were based upon the assumption that spontaneous recovery slows down during the chronic phase and therefore any benefit observed during this phase is likely a result of rTMS treatment. In addition, owing to the fact that it is difficult to recruit patients with sustained, chronic deficits after they have left the hospital or rehabilitation care, most studies with larger sample sizes and those that were RCTs included subacute population (Khedr et al. 2014; Seniow et al. 2013; Heiss et al. 2013), rather than chronic, with a few exceptions like Barwood et al. (2013).

Table 7.1 D&B quality checklist for included rTMS treatment studies separated by study designs

		D&B subscales				
Study names	Total score (max = 31)	Reporting (max = 11)	External validity (max = 3)	Internal validity bias (max = 7)	Internal validity confounding (max = 6)	Power (max = 5)
	Between-subject/RCTs					
Barwood et al. (2013)	22	7	1	7	5	3
Heiss et al. (2013)	20	8	1	6	5	5
Khedr et al. (2014)	28	10	1	7	6	5
Seniow et al. (2013)	30	11	1	7	6	5
Mean	**25.0**	**9.0**	**1.0**	**6.7**	**5.5**	**4.5**
SD	**4.76**	**1.83**	**0.00**	**0.50**	**0.58**	**1.00**
	Crossover trials					
Kindler et al. (2012)	28	11	1	7	5	5
Medina et al. (2012)	24	11	1	6	3	3
Mean	**26.0**	**11.0**	**1.0**	**6.5**	**4.0**	**4.0**
SD	**2.83**	**0.00**	**0.00**	**0.71**	**1.41**	**1.41**
	Within-subject/pre-post					
Abo et al. (2012)	21	10	1	3	2	5
Kakuda et al. (2011)	16	9	0	4	1	2
Szaflarski et al. (2011)	22	11	1	4	2	4
Mean	**19.7**	**10.0**	**0.7**	**3.7**	**1.7**	**3.7**
SD	**3.21**	**1.00**	**0.58**	**0.58**	**0.58**	**1.53**

Taking into account these different aspects from the methodological quality checklist, we posit that treatment effects between different study designs should be interpreted with caution as the patient inclusion criteria, particularly the time since stroke, differed considerably in these studies.

7.3.3 Evidence Surrounding the Use of rTMS for Aphasia

Our goal in this section is to draw together all the topics that we have discussed so far to examine the evidence surrounding the use of rTMS in treating poststroke aphasia. In this section, first, we will briefly revisit the evidence of the treatment effects of rTMS in both RCTs and non-RCTs. Based on the evidence at hand, we

will evaluate our confidence in this treatment as it stands and provide our recommendation for its readiness in large-scale, clinical applications in PWA.

Table 7.2 provides a summary of the treatment studies, including information about the patient demographics, their clinical characteristics such as stroke and aphasia types, details regarding the rTMS protocols, and the relevant findings; refer to Table 7.1 for D&B quality ratings for the studies discussed in this section.

Two relatively large RCTs in subacute PWA population—Heiss et al. (2013; $n = 29$) and Seniow et al. (2013; $n = 40$)—scored high on quality ratings (20 and 30, respectively) with only minor differences between these studies in the applied rTMS protocols (Seniow et al. 2013; Heiss et al. 2013). While Heiss et al. (2013) provided low-frequency rTMS over 10 days, 20 min per day, Seniow et al. (2013) provided rTMS over 15 days for 30 min per day. In both studies the active stimulation site was PTr in the right hemisphere. While Heiss and colleagues (2013) compared rTMS treatment over the right PTr with that of stimulation over the vertex, Seniow and colleagues (2013) compared rTMS treatment over right PTr with sham stimulation that was provided on the same site; in both studies the stimulation intensity was 90 % of each individual patients' resting motor thresholds (rMT). Heiss et al. (2013) reported significant improvement on a global severity measure of aphasia (AAT) in the real group compared to the control group, while Seniow et al. (2013) did not observe any measurable difference between the real and the sham groups. The latter study did report improvement in a subpopulation of patients who suffered from severe aphasia in the real compared to the sham group. Although minor differences in the rTMS treatment protocol existed between these two studies, it is unclear why one group reported significant improvement while the other group did not. In fact, the dosage of rTMS was greater in Seniow et al., the study that did not find rTMS-specific treatment effects. Perhaps in this case, clinical factors such as the lesion size and location, which were not explicitly discussed in these studies, may have played a critical role. In addition, these findings suggest that patients exhibiting severe language deficits may selectively respond to rTMS treatment more than those with mild or moderate deficits. Overall, the treatment effects of rTMS in the subacute PWA population need further verification. These studies also bring up an important knowledge gap in this field—a lack of investigations dedicated to understanding the relationship between rTMS dosage and response in PWA.

A RCT conducted in chronic patients—Barwood et al. (2013; $n = 12$)—showed significant increases in naming, in expressive language, and even in auditory comprehension in the real compared to the sham group 2 months following the end of stimulation (Barwood et al. 2013). In this study, the researchers also targeted the right hemispheric PTr site using low-frequency rTMS for 10 days, 20 min per day using stimulation intensity that was individually defined at 90 % of rMT. This is the only RCT in our knowledge to have included and shown significant improvements in chronic PWA after the rTMS treatment.

Two studies that were conducted using a crossover design—Kindler et al. (2012; $n = 18$) and Medina et al. (2012; $n = 10$)—also reported significant increases in language abilities including spontaneous speech and picture naming, specifically after patients received real stimulation compared to the sham stimulation (Kindler et al.

Table 7.2 Summary of intervention studies for poststroke aphasia using rTMS

Study name		*N*	Stroke onset	Age (years)	Aphasia/stroke characteristics	Study design	Methods	Stimulation site	Outcome measures; *findings*
1.	Barwood et al. (2013)		Chronic		Nonfluent, global Left MCA infarct	Between RCT	1 Hz; 90 % RMT; 10 days; 20 min/day	Right PTr	BNT, BDAE, picture naming *Naming, expressive language and auditory comprehension improved up to 12 months in the real compared to the sham group*
		6 real	3.5 ± 1.3 y	60.8 ± 6.0					
		6 sham	3.5 ± 1.5 y	67 ± 13.1					
2.	Heiss et al. (2013)		Subacute		Broca, Wernicke, global, amnestic Left MCA infarct	Between RCT	1 Hz; 90 % RMT 10 days; 20 min/day 45 min of SLT PET	Right PTr or vertex	AAT *Change in global AAT scores in right-handed patients was higher in the real compared to the sham group*
		15 real	39.7 ± 18.4 d	68.5 ± 8.2					
		14 sham	50.1 ± 24.0 d	69.0 ± 6.3					
3.	Seniow et al. (2013)		Subacute		Broca, Wernicke, transcortical, mixed Left ischemic	Between RCT	1 Hz; 90 % RMT 15 days; 30 min/day 45 min of SLT	Right PTr	BDAE; ASRS *No notable difference observed between groups, but patients with severe aphasia in the real group selectively improved on repetition submeasure compared to the sham group*
		20 real	33.5 ± 24.1 d	61.8 ± 11.8					
		20 sham	39.9 ± 28.9 d	59.7 ± 10.7					

4.	Khedr et al. (2014)		Subacute		Nonfluent, mixed (perceptive and nonfluent) Left thromboembolic infarction MCA	Between RCT	1 and 20 Hz applied sequentially over right and left hemispheres, respectively 110 % RMT	Right PTr and POp Left PTr and POp	ASRS; HSS *No significant baseline differences between groups; significant improvement in ASRS and HSS language scores in the real sham rTMS, which was sustained at both follow-up sessions*
		19 real	5.8 ± 4.1 w	61.0 ± 9.8					
		10 sham	4.0 ± 2.6 w	57.4 ± 9.6					
5.	Kakuda et al. (2011)	4 real only	Chronic 68.2 ± 46.6 m	50.7 ± 9.5	Motor-dominant aphasia Left ICH	Within	10 min of 6 Hz followed by: 20 min of 1 Hz; 90 % RMT 11 days; 2 sessions/day 60 min of SLT	Right IFG	SLTA, J-WAB; *All patients showed at least a 5 % increase in correct answer rate in both SLTA and J-WAB following treatment. Three patients showed a 15 % increase in correct answer rate on the SLTA*
6.	Szaflarski et al. (2011)	8 real only	Chronic 5.3 ± 3.6 y	54.4 ± 12.7	Broca, Wernicke, global Left MCA	Within	iTBS (3 pulses at 50 Hz) 10 days; 200 s/day 80 % AMT fMRI-guided	Left PTr	BNT, SFT, COWAT, PPVT, mini-CAL, BDAE CompId *There was a significant improvement in semantic fluency and a trend toward significance in the self-report mini-CAL following iTBS*

(continued)

Table 7.2 (continued)

Study name		*N*	Stroke onset	Age (years)	Aphasia/stroke characteristics	Study design	Methods	Stimulation site	Outcome measures; *findings*
7.	Abo et al. (2012)	24 real only	Chronic 34.7 ± 20.5 m	55.9 ± 8.8	Nonfluent, fluent Left infarction and ICH	Within	1 Hz; 90 % RMT 10 days; 40 min/day 60 min of SLT; fMRI (right or left) and aphasia type (STG or IFG)-guided	Right or left STG; right or left IFG	SLTA, J-WAB *Nonfluent aphasia group did not improve on SLTA-ST or WAB (short-term—immediately after treatment), but did improve in SLTA and spontaneous speech (long-term—4 weeks after treatment) following rTMS treatment. Fluent aphasia group improved on WAB (short-term) and SLTA and auditory and reading comprehension (long-term) following treatment*
8.	Medina et al. (2012)	5 real 5 sham	Chronic 49.8 ± 29.6 m 58.6 ± 34.8 m	60.6 ± 7.1 62.6 ± 10.1	Nonfluent Left ischemic stroke	Crossover	1 Hz; 90 % RMT 10 days; 20 min/day Optimal site finding	Right IFG	BDAE, BNT, narrative speech production; picture naming (unpublished) *Significant increase in multiple measures of discourse productivity following rTMS compared to baseline. No significant increase in sentence production or grammatical accuracy. No significant performance difference following sham TMS*

9.	Kindler et al. (2012)	18 real/ sham	Subacute and chronic 16.9 ± 18.3 m	55.0 ± 8.6	Broca, anomic, speech apraxia Left ischemic and hemorrhagic	Crossover	cTBS (3 pulses at 30 Hz) 2 days—sham/real; 44 s/day	Right PTr	Timed picture naming, alertness task *Naming performance was better and naming latency shorter following TBS compared to sham treatment. Patients in the subacute stroke phase responded best to the treatment*

Abbreviations: *ICH* intracerebral hemorrhage, *d* days, *m* months, *y* years, *MCA* middle cerebral artery, *ICA* internal carotid artery, *RMT* resting motor threshold, *AMT* active motor threshold, *cTBS* continuous theta burst stimulation, *SLT* speech and language therapy, *PTr* pars triangularis, *POp* pars opercularis, *IFG* inferior frontal gyrus, *STG* superior temporal gyrus

2012; Medina et al. 2012). In Kindler et al. (2012), both subacute and chronic patients were included, while in Medina et al. (2012), only chronic patients were included. The rTMS protocols applied in these studies were also different in that while Kindler et al. (2012) delivered cTBS, 1 Hz rTMS was delivered as real treatment in Medina et al. (2012); both studies targeted right hemispheric sites in the IFG. Although these two forms of rTMS are fundamentally different with respect to how they impact underlying cortical areas, evidence suggests that they both have disruptive or inhibitory aftereffects (e.g., Huang et al. 2005). The site localization methods used in these studies were also distinct: while a precise and optimal site-finding protocol was adopted by Medina et al., Kindler et al. used cranial landmarks and 10–20 international system to localize right PTr in all patients. Notably for nine out of ten patients in Medina et al. (2012), the optimal site was a site within the right PTr (ventral posterior PTr; Fig. 7.1). Despite these differences in methodology, both studies reported statistically significant group-averaged improvements, selectively after real rTMS compared to sham.

Two recent studies adopted a within-subject design to examine novel intervention approaches using rTMS. In one study (Abo et al. 2012), the goal was to examine a novel site-finding approach for providing the low-frequency rTMS treatment over right frontal or temporal sites. We discussed the fMRI-driven site-finding protocol employed by Abo et al. (2012) earlier, whereby stimulation sites were identified based on correlational activation patterns during a language task and also based on the type of language deficits exhibited by patients. The other novel study (Szaflarski et al. 2011) was designed to examine a theoretical model for inducing language recovery by facilitating perilesional recruitment using an excitatory, rather than low-frequency inhibitory rTMS protocol. Szaflarski et al. (2011) is the only treatment study in PWA to our knowledge to have applied iTBS protocol on the damaged left hemispheric frontal areas. Using these novel approaches, both Abo et al. (2012) and Szaflarski et al. (2011) reported significant increases in language performance based on selected outcome measures. In nonfluent patients, Abo et al. (2012) reported improvement in spontaneous speech lasting at least 4 weeks; they also reported improvement in fluent patients on auditory comprehension that lasted at least 4 weeks, as well as improvement on a global measure of aphasia severity. Szaflarski et al. (2011) reported improvements on a semantic fluency task and also a tendency toward better self-reported communication abilities.

7.3.4 GRADE System to Evaluate the Strength of Recommendation in Favor of rTMS in PWA

Given the evidence presented in the earlier section and using the D&B quality checklist in Table 7.1, we can have applied the GRADE system to determine the strength of our recommendation in favor of the rTMS treatment (Guyatt et al. 2008). Specifically, we used the four factors described in Guyatt et al. (2008) to make our recommendation: (1) balance between desirable and undesirable effects, (2) quality of evidence, (3) values and preferences, and (4) costs (Guyatt et al. 2008).

None of the studies discussed in this section or the ones summarized in Table 7.2 reported severe adverse events in their patients, including seizures, which are the most serious adverse event that has historically been associated with rTMS treatment protocols. In addition, numerous recent studies in patient populations (Bae et al. 2007) and healthy individuals that have followed published safety guidelines for rTMS administration (Rossi et al. 2009; Wasserman 1998; Bolognini et al. 2009) suggest that rTMS is extremely well-tolerated and there are no reports of long-term ill effects of stimulation. While there are well-established safety guidelines for standard 1 Hz/low-frequency rTMS, a similar set of safety parameters has not yet been established for TBS, since this approach is still relatively new. However, evidence suggests that by adhering to the parameters described in the landmark papers describing TBS, ill effects can be avoided (Oberman and Pascual-Leone 2009). Overall, there appear to be only minor undesirable consequences of using 1 Hz/low-frequency rTMS relative to the potential long-term benefits of treatment in PWA. However, more research is warranted to define safety guidelines for newer techniques like TBS before they are applied broadly to PWA.

Based on methodological quality assessments, we conclude that there is substantial and high-quality evidence in favor of low-frequency/1 Hz rTMS on right hemispheric frontal sites, particularly the right PTr. However, as discussed in earlier sections, there is a great deal of heterogeneity across studies with respect to rTMS methodologies and study designs, which somewhat weakens our confidence in this evidence. In addition, the impact of individual variability in clinical factors on response to rTMS across PWA is largely unknown. Theoretical models of recovery and our own work using site-finding protocols suggest that a "one-size-fits-all" rTMS protocol may not be the most effective approach to treating PWA. There is also a dearth of data for us to comment on the impact of rTMS on functional deficits in communication, patient quality of life, and patient satisfaction with treatment.

Lastly, compared to other noninvasive brain stimulation techniques, TMS and its ancillary equipment can be expensive and require patients and their families to make frequent visits to a research laboratory or clinical facility. For the sake of comparison, it is worth noting that 4–6 weeks of rTMS treatment in depression cost as much as $10,000. Moreover, insofar as stroke rehabilitation is not an FDA-approved indication for rTMS, it is likely that insurance companies will not cover these costs, at least in the immediate future (e.g., see www.aetna.com/cpb/medical/data/400_499/0469.html). Although some preliminary evidence suggests that rTMS may produce long-term benefits for PWA, it remains unclear whether or not maintenance treatments will be necessary and how frequently they will need to administered, adding to the overall costs.

Considering that there is still much to be learned about this technique, we are currently inclined toward a weak recommendation for clinical use, specifically in favor of low-frequency/1 Hz rTMS over right hemispheric sites. Moreover, based on the evidence presented in this chapter and our own work, the specific sites of stimulation should vary between individuals based on manifest language deficits and/or other clinical factors associated with stroke. We recommend further

investigation of rTMS in the context of research in large-scale randomized phase II and phase III clinical trials.

7.3.5 Guidelines for Future Clinical Trials

In this section, we provide guidelines for designing future clinical trials with the specific goal of overcoming the heterogeneity that exists in the current rTMS treatment literature. We recommend that researchers take into account the following parameters that we believe will strengthen the evidence further and allow more confidence and stronger recommendations in favor of clinical applications of rTMS in aphasia.

7.3.5.1 Use of Clinically Relevant Outcome Measures

One of the primary goals of translational and clinical research in neurorehabilitation is that novel treatments should not only improve performance on controlled neuropsychological tasks but also the function of neural systems in ways that ultimately result in favorable changes in quality of life (Robertson and Fitzpatrick 2008; Shah et al. 2013). Picture naming, the most commonly used outcome measure in treatment studies evaluating rTMS in aphasia, is a useful neuropsychological test of language performance, but the field needs to move well beyond it. Only a few studies thus far have evaluated whether improved performance on neuropsychological batteries translates into meaningful benefit in patients' ability to communicate with their loved ones. For instance, one study reported a trend toward improvement in self-reported Communicative Activities Log after rTMS treatment (Szaflarski et al. 2011). Our group examined whether individualized rTMS treatment facilitates discourse production, whereby we captured rTMS-induced benefits in various aspects of language production that contribute to fluent speech (Medina et al. 2012). Primary or secondary outcome measures in ongoing and recently completed clinical trials of rTMS treatment in aphasia also lack ecological tests of language production. As we hone in on optimizing rTMS parameters for the treatment of aphasia, it will be crucial to examine whether rTMS augments patients' overall ability to communicate and the broader impact that this has on their lives.

7.3.5.2 RTMS Protocols

Throughout this chapter, we have made a case against a monolithic rTMS treatment approach in favor of an individualized approach that is informed by mechanism(s) of recovery on a patient-by-patient basis (Abo et al. 2012; Medina et al. 2012; Naeser et al. 2005). However, practically speaking, this approach is difficult to achieve, considering the current status of our knowledge regarding the differences in recovery mechanisms across patients.

The impact of clinical factors such as stroke volume and location on responsiveness to different rTMS protocols is understudied (Anglade et al. 2014). The handful of studies that have examined these relationships suffer from statistical power issues because of small sample sizes, limiting their ability to provide findings that can be generalized to all aphasic patients (Martin et al. 2009). In addition to cortical gray

matter injury, emerging evidence also suggests that the extent of damage along the white matter tracts that connect language regions also critically influences the reorganization of bilateral language networks reorganization after stroke (Forkel et al. 2014; Tak and Jang 2014). Placing this within the framework of aphasia recovery mechanisms presented earlier in this chapter, it may be the case that patients with small strokes and less severe injury to white matter may selectively benefit from excitatory rTMS protocols that target residual left hemispheric areas, while patients suffering from larger strokes that are more likely to suffer from severe white matter damage may benefit from approaches that increase the efficiency of interhemispheric networks, possibly by focused inhibition of particularly noisy nodes (e.g., right PTr). In addition to lesion profiles, the type of language deficits patients experience may also predict the relative roles of left and right hemisphere areas in recovery and must be considered when planning rTMS treatments. Stroke chronology is another important clinical factor that profoundly impacts neuroplastic changes. Depending on the time frame for treatment, the role of reorganizing brain regions might be different, potentially militating for different rTMS approaches in different clinical populations.

Although one of the major theoretical advantages of using rTMS to treat disorders like aphasia is that the technique is capable of inducing highly focal and specific alterations in brain function, the tools and approaches that have been used to target stimulation have not been standardized. The use of cranial landmarks and 10–20 international system to localize sites for rTMS, especially around damaged left perisylvian areas is not likely to be practical moving forward. Differences in baseline neuroanatomy across subjects and substantial distortions in that anatomy due to stroke suggest that a system for guiding stimulation that is based on measurement of external cranial landmarks lacks the precision that is required for therapeutic rTMS administration. Moreover, locating sites by cranial landmarks does not take advantage of the high spatial resolution of rTMS compared to other noninvasive brain stimulation approaches. When paired with the appropriate technique for targeting stimulation, the high spatial resolution of rTMS may allow for manipulation of specific areas deemed critical for language recovery. For instance, according to the model suggesting that only a limited number of sites within in the right hemisphere are noisy and maladaptive to recovery, it is crucial to focally inhibit these sites and not the surrounding sites that may in fact be contributing positively to language recovery. Therefore, optimal site localization procedures, informed by functional activation patterns or by rTMS-driven changes in language performance, are likely an improvement over non-localized applications and may ultimately prove more practical.

These claims will need to be confirmed in future clinical trials that are individualized with respect to both clinical and rTMS-specific characteristics to systematically stratify rTMS response in different patients. This information in turn will guide future attempts at individualizing not only location but also the type of rTMS (inhibitory, excitatory, dual) to be applied based on individual patients' needs. In summary, variability in a range of factors we have discussed, including neural mechanisms of spontaneous language recovery, lesion anatomy and chronology, and baseline neuroanatomic characteristics, warrants a multifactorial and individualized approach to designing rTMS treatment studies of aphasia.

7.3.5.3 Study Duration and Size

There is also a clear need to quantify the duration for which focal manipulation of cortical networks results in improved language functions beyond the period of treatment. Relatively few studies have examined the effects of rTMS over monthly or yearly follow-ups, which poses an important obstacle in determining the ability of rTMS to induce long-term therapeutic benefits. Future clinical trials will need to characterize the longitudinal benefits of rTMS in aphasia. As this information is made available, we may need to make adjustments to the rTMS dosage, either by increasing the duration of treatment or by repeating treatment periodically (c.f. current FDA-approved rTMS protocols for depression) (Neurodiagnostic and Neurotherapeutic Devices Branch 2011). In addition to clarifying the duration of rTMS effects, future trials also need to clarify whether there is an optimal phase (i.e., acute, subacute, or chronic) for the application of rTMS. As discussed earlier, different rTMS protocols may be required depending on the time frame being targeted after stroke. Better understanding of the cascading functional and structural changes associated with different phases of spontaneous language recovery may help to refine the administration of different rTMS protocols in the future. Finally, current studies have been limited in the number of enrolled patients. For rTMS treatment to be made available in clinical settings, more definitive multicenter trials enrolling large numbers patients will be necessary.

Conclusions

In this chapter, we discussed theoretical neural changes that take place in the language network in PWA after strokes that mediate spontaneous language recovery. These neuroplastic changes are largely shaped by the extent of brain injury and by loss of connectivity among key language areas. Evidence suggests that along with areas within the injured hemisphere, homotopic areas within the uninjured hemisphere are recruited in the brain's attempt to enable language recovery; however whether these areas act to induce or impede recovery is not clear. Rather than describing the role of uninjured hemispheric areas in absolute terms (i.e., compensatory versus maladaptive), recent research suggests that their involvement may be multidimensional, whereby some areas may be involved in a compensatory capacity while others may be maladaptive. The precise role of these areas remains an area of active investigation.

Therapeutic applications of rTMS in poststroke aphasia have capitalized on a growing but incomplete understanding of these neuroplastic changes, in order to guide the location and type of stimulation administered. Most rTMS studies have applied stimulation over areas that are either within the injured or the uninjured hemisphere, with the goal of either inhibiting or facilitating activation in these areas, respectively. There have also been a few applications of rTMS that seem to fall outside of this basic conceptual framework. Evidence from a variety of treatment studies suggests that rTMS can significantly augment performance on a variety of language functions. Overall, this growing body of data has demonstrated that rTMS is a powerful tool in aphasia research because it not only allows us to enhance our understanding of the neural basis

of language systems and language disorders but also because it can directly leverage this understanding in order to provide a novel and promising treatment.

Further, we acknowledge that the use of rTMS in the field of aphasia rehabilitation has come a long way from initial attempts to validate its feasibility in small case studies enrolling 1–2 PWA to relatively large treatment studies enrolling dozens of patients. However, one of the biggest obstacles yet to overcome is the absence of larger-scale longitudinal clinical trials that would support the introduction of this tool into broader clinical practice. In these future trials, the goal should not be simply to validate the efficacy of this technique using simple language measures but also to systematically evaluate whether individualized rTMS treatment mediates sustained improvements in everyday communication and in overall quality of life. The most important point that we wish to convey in this chapter is that aphasic patients are not all identical and therefore the rTMS treatments administered should also not be identical. Surprisingly, although several sources of interindividual variability are known to exist, empirical evidence highlighting the impact of these differences across patients on rTMS treatment is largely lacking. Stratification of patients should be a key feature of future treatment trials to fully characterize how clinical variables impact response to rTMS and how modifications to rTMS protocols can be informed by individual patients' needs.

A decade since rTMS was first reported as a potential treatment for aphasia, it is no longer novel to claim that a particular rTMS protocol simply "worked" in improving performance in a group of patients. As we have described at length, there is already a strong evidence to support this claim. What the field requires moving forward is to formulate ways to strengthen this evidence further and to determine how this technique can be tailored to the needs of different types of PWA so as to help them perform better on their everyday communication needs. Devising a more systematic and comprehensive approach is by no means a trivial task. Given the wide range of clinical presentations and contributing factors in aphasia, the notion of individualizing treatment runs the potential risk of producing too many different solutions. Nonetheless, as a first step in the right direction, a theory-driven, iterative, and multifactorial approach can be applied to substantiate a few classes of characteristics that can be used to refine treatment approaches using rTMS. As this iterative process of probing and treating continues, we are hopeful that our understanding of the neuroplastic processes that occur in PWA and our ability to treat poststroke language deficits will continue to make great strides.

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rTMS in Visual Hemineglect After Stroke

8

René M. Müri

Abstract

This chapter presents an overview of the literature of clinical application of TMS in the treatment of visual hemineglect. Eleven studies were found. In general, inhibitory protocols (low-frequency repetitive TMS, rTMS, or continuous theta burst stimulation, cTBS) were used to stimulate the contralesional intact hemisphere. The quality of evidence of the different studies is heterogeneous ranging from single case reports to randomized, blinded, and sham-controlled studies. Repetitive TMS is safe; no serious side effects were reported. There is a clear advantage for the use of inhibitory rTMS protocols such as cTBS. At the moment, a week recommendation based on the GRADE system is given for cTBS protocols with repeated daily applications as described in the study of Cazzoli et al. (Brain 135:3426–3439, 2012). This protocol has also a low burden for the patient due to the short duration of the stimulation and the duration of the whole therapy limited to 2 days. The effects on visual hemineglect are long lasting, more than 3 weeks. The improving effects are not only found on a neuropsychological test level but also on daily activities of the patient.

8.1 Introduction

Neglect is defined as a multimodal deficit in detecting, responding, or orienting toward stimuli located in the contralateral side of a brain lesion (Heilman et al. 2003). Typically, such patients ignore the stimuli in the contralateral visual field and are, for example, not able to copy a figure (see Fig. 8.1). In acute stroke, visual hemineglect is common, especially after a right-hemispheric lesion, being found in up to 43 % of patients (Ringman et al. 2004). It is estimated that three to five million new cases of neglect may occur worldwide per year (Appelros et al. 2003; Corbetta et al. 2005; Pedersen et al. 1997). Neglect patients have a slower functional recovery and a reduced

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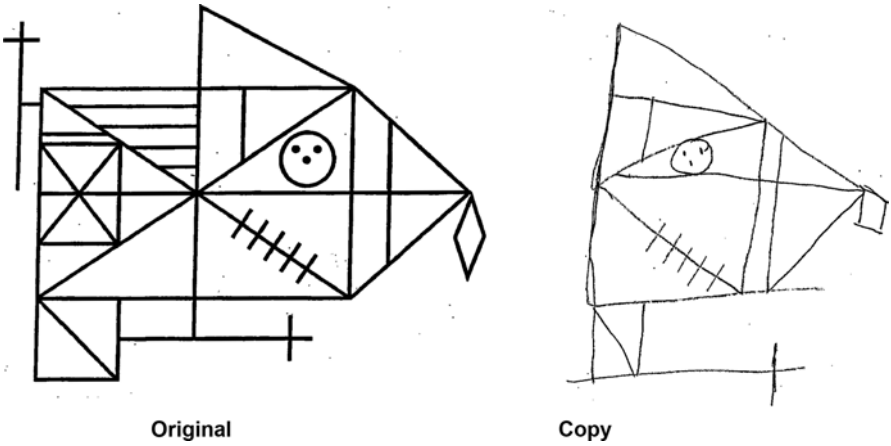

Fig. 8.1 Visual hemineglect in copying Rey figure. The patient largely ignores the *left side* of the figure and copies only parts of the *right side*

ability to cope with the activities of daily living and generally need longer neurorehabilitation (Buxbaum et al. 2004; Cherney et al. 2001; Di Monaco et al. 2011; Gillen et al. 2005; Katz et al. 1999; Stone et al. 1992), which has also consequences for the health care system (Paolucci et al. 2001; Wee and Hopman 2008).

Finally, neglect is an independent predictor of poor rehabilitation outcome, in terms of more limited functional independence (Stone et al. 1992; Di Monaco et al. 2011) and lower likelihood of being discharged home (Wee and Hopman 2005, 2008).

Depending on the applied assessment tools, the reported incidence of neglect widely varies between 10 and 82 % following right-hemispheric lesions and between 15 and 65 % following left-hemispheric lesions (for a review, see Plummer et al. 2003).

Noninvasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), is one of the different therapeutic strategies to treat neglect that have been evaluated so far. Visual scanning training, prism adaptation, neck muscle vibration, sensory stimulation, and optokinetic stimulation have also been tested (for a review, see Bowen et al. 2002; Kerkhoff and Schenk 2012). These approaches have been shown to reduce the severity of neglect. However, they are often difficult to use in a rehabilitation setting – particularly during the acute or subacute phase of stroke – due to the short duration of their effects, patient discomfort, or the difficulty for patients to cooperate, as mentioned by Fierro and colleagues (2006).

8.2 The Concept of Interhemispheric Rivalry in Hemineglect

The interhemispheric rivalry concept by Kinsbourne (1987, 1993) is so far very influential for the application of rTMS in neglect. According to this concept, the parietal cortices compete to direct attention toward the contralateral space, thereby exerting a reciprocal interhemispheric inhibition. A damage to the right parietal cortex causes a disinhibition of the intact, left parietal cortex and thus a hyperactivation of the latter. This hyperactivation triggers an increased inhibition on the

damaged hemisphere, further depressing the neural activity in the latter. These dynamics result in a rightward, ipsilesional attentional bias. Evidence supporting this concept comes from several sources, including animal studies, correlational fMRI studies in humans, and interventional TMS studies. Several animal studies (e.g., Sprague 1966; Payne and Rushmore 2004; Rushmore et al. 2006; Valero-Cabré et al. 2006) showed that unilateral inhibitory interventions introduce an imbalance in the physiological activity between the networks controlling visuospatial attention in the two hemispheres, favoring the intact hemisphere and leading to visual neglect. The reduction of this imbalance (and, as a consequence, of the visual neglect) is possible through the reduction of the hyperexcitability of specific cortical or subcortical regions in the intact hemisphere, by a lesion or cooling.

In humans, functional magnetic resonance imaging (fMRI) studies showed a relative hyperactivity of the left, undamaged hemisphere in neglect patients, which correlated with the severity of the disorder (Corbetta et al. 2005). The recovery of neglect correlated with the restoration and rebalancing of the activity between the damaged and the undamaged hemisphere, particularly in the dorsal parietal cortices (Corbetta et al. 2005; He et al. 2007). Finally, Koch and colleagues (2011, 2012) demonstrated a pathological hyperexcitability of the intact, contralesional area in neglect patients by means of a twin-coil TMS technique. They assessed the excitability within parieto-motor cortical circuits and showed a significantly higher left-hemispheric excitability in neglect patients as compared to healthy controls or to patients with right-hemispheric lesions but no neglect. This hyperexcitability was also significantly correlated with neglect severity. The application of inhibitory rTMS over the left, contralesional posterior parietal cortex significantly reduced the hyperexcitability of this area, as measured by motor evoked potentials (MEP), and resulted in a significant reduction of neglect severity.

8.3 Methods

The following databases were searched for studies published in English: PubMed, PsycINFO, and ScienceDirect. The following search terms were used: neglect, visual neglect, unilateral neglect, rehabilitation, and TMS. Furthermore, previous reviews concerning treatment of hemineglect by rTMS were consulted (Cazzoli et al. 2010; Hesse et al. 2011; Müri et al. 2013; Schulz et al. 2013; Yang et al. 2013). Studies were included in the review if they satisfied the following criteria: use of an offline TMS protocol, treatment of hemineglect, or evaluation of the duration of TMS effects on hemineglect, as a goal of the study.

8.4 Calculation of TMS Treatment Effect Sizes and Levels of Evidence

Since treatment effects between an intervention and a control group were rarely reported in the studies, we calculated the relative magnitude according to the data presented in the publications. For data collected with repeated measures

designs (Brighina et al. 2003; Cazzoli et al. 2012; Koch et al. 2011; Kim et al. 2010; Nyffeler et al. 2009; Song et al. 2009), we used the F-ratios and the degrees of freedom provided in the respective publications (degrees of freedom were either provided or had to be calculated) in order to calculate the effect size measure r by applying Andy Field's formula (2009). For independent-group pretest–posttest designs, where statistical data was presented in gain scores (Kim et al. 2013; Lim et al. 2010), the effect size measure d was computed using Morris and DeShon's method (2002). Finally, for the purpose of comparison, these effect sizes were rated according to the guidelines for r and d, respectively (Field 2009).

The level of evidence of the studies was evaluated according to the guidelines of the OCEBM Levels of Evidence (http://www.cebm.net/ocebm-levels-of-evidence/).

8.5 Results

We found ten studies that used rTMS for visual hemineglect treatment. A total of 133 patients were involved. The number of patients included in the studies varied considerably, from a single case report (Bonni et al. 2013) to 27 patients (Kim et al. 2013). The overview of the studies is presented in Table 8.1.

8.5.1 rTMS Protocols

All studies used inhibitory protocols, such as low-frequency rTMS (i.e., 1 Hz or below) or continuous theta burst stimulation (cTBS; with 50 or 30 Hz bursts). Five studies used low-frequency rTMS (Brighina et al. 2003; Shindo et al. 2006; Koch et al. 2011; Song et al. 2009; Lim et al. 2010), with frequencies of 0.5, 0.9, or 1 Hz, applied over the contralesional hemisphere. Seventy-nine patients took part in these studies. Furthermore, Kim and colleagues (2010; 2013) compared the effects of low-frequency rTMS over the contralesional hemisphere with those of high-frequency rTMS (20 Hz) over the ipsilesional hemisphere. Four studies, which included 35 patients in total, used cTBS (Nyffeler et al. 2009; Cazzoli et al. 2012; Koch et al. 2012; Bonni et al. 2013) over the contralesional hemisphere. The number of rTMS pulses varied between 450 (Song et al. 2009) and 1200 pulses (Kim et al. 2010; 2013) per session; the cumulative number varied between 1602 (Nyffeler et al. 2009) and 12,600 pulses (Song et al. 2009). The intervention duration varied between a single session (Kim et al. 2010) and 28 sessions (Song et al. 2009; Bonni et al. 2013). With the exception of two studies that used a round coil (Nyffeler et al. 2009; Cazzoli et al. 2012), all other studies used a focal, figure-of-eight coil. Nine studies explicitly reported that there was no harm or side effects of rTMS application. In one study (Kim et al. 2001), side effects were not mentioned.

Table 8.1 Characteristics of the studies

Author	Year	No. of patients (no. of males)	Etiology	Mean age (SD)	Mean time post (SD)	Additional rehabilitation therapy	Sham/ control (no.)	Stimulation site	Coil used	No. of pulses per session frequency intensity	No. of stimulation sessions
Brighina et al.	2003	3 (3)	Ischemia	52 (5.5)	4 months (1.2)	No	No/(5)	Contra (P5)	Figure 8	900 1 Hz 90 % MT	One session, every 2nd day
Shindo et al.	2006	2 (1)	Ischemia	60 (1)	175 days, 186 days	Yes	No	Contra (P5)	Figure 8	900 0.9 Hz 95 % MT	One session, three times per week
Nyffeler et al.	2009	11 (na)	Ischemia/ hemorrhage	54 (8.7)	7 months (13.0)	Yes	Yes/(5)	Contra (P3)	Round coil	801 TBS 30 Hz 100 % MT	Two sessions per day Four sessions per day
Song et al.	2009	14 (8)	Ischemia/ hemorrhage	56 (9.0) 64 (12.6)	38 days (15.2) 32 days (11.5)	Yes	Yes/(7)	Contra (P3)	Figure 8	450 0.5 Hz 90 % MT	Two sessions per day
Kim et al.	2010	19 (10)	Ischemia	62 (11.2)	24 months (12.3)	Na	Yes	Contra (P3), ipsi (P4)	Figure 8	1200 1 Hz contra/20 Hz ipsi 90 % MT	One session
Lim et al.	2010	14 (4)	Ischemia/ hemorrhage	72 (5.3) 66 (15.2)	62 days (111.1) 139 days (194.8)	Yes	No/(7)	Contra (P5)	Figure 8	900 1 Hz 90 % MT	One session, five times per week

Table 8.1 (continued)

Author	Year	No. of patients (no. of males)	Etiology	Mean age (SD)	Mean time post (SD)	Additional rehabilitation therapy	Sham/ control (no.)	Stimulation site	Coil used	No. of pulses per session frequency intensity	No. of stimulation sessions
Cazzoli et al.	2012	24 (17)	Ischemia/ hemorrhage	58 (2.3)	27 days (4.4)	Yes	Yes/(8)	Contra (P3)	Round coil	801 TBS 30 Hz 100 % MT	Two sessions per day
Koch et al.	2012	18 (10)	Ischemia	61 (13.0) 72 (4.9)	50 days (29.4) 37 days (10.5)	Yes	Yes	Contra (P3) neuronavigation	Figure 8	600 TBS 50 Hz 80 % MT	One session, five times per week
Kim et al.	2013	27 (15)	Ischemia	69 (14.4) 64 (10.3) 68 (6.5)	14 days (4.7) 14 days (3.6) 16 days (8.5)	Yes	Yes	Contra (P3), ipsi (P4)	Figure 8	1200 1 Hz 90 % MT 1000 20 Hz 90 % MT	One session, five times per week
Bonni et al.	2013	1 (1)	Brain trauma	20	24 months	No	No	Contra (P3)	Figure 8	600 TBS 50 Hz 80 % MT	Two sessions per day

Abbreviations: *ADL* activities of daily living, *BI* Barthel Index, *BIT* behavioral inattention test, *BIT-C* conventional, *BIT-B* behavioral, *BRS* Brunnstrom recovery stage, *HDS-R* revised Hasegawa dementia scale, *MMSE* mini-mental state examination, *PVT* peripheral visual targets, Vienna Test System, *MVPT* motor-free visual perception test, *CBS* Catherine Bergego Scale, *K-MBI* Korean-modified Barthel Index

8.5.2 Localization of Target Region

Nine studies located the target stimulation site using the international 10–20 EEG system. In seven studies, P3 was targeted. Two studies targeted in addition P4 for high-frequency, excitatory stimulation (Kim et al. 2010, 2013). Two other studies stimulated over P5 (Brighina et al. 2003; Shindo et al. 2006). Only one study used a neuronavigation system (Koch et al. 2012). In this study, the left PPC was targeted, positioning the coil over the angular gyrus, close to the posterior part of the adjoining intraparietal sulcus, based on individual anatomic MRI scans.

8.5.3 Control Conditions and Additional Therapy

Five studies were sham controlled (Nyffeler et al. 2009; Kim et al. 2010, 2013; Cazzoli et al. 2012; Koch et al. 2012); the remaining five studies had no sham control group. Two studies (Song et al. 2009; Lim et al. 2010) included a control group of patients without neglect. Concerning additional rehabilitation interventions, in four studies (Shindo et al. 2006; Song et al. 2009; Cazzoli et al. 2012; Kim et al. 2013) the patients with hemineglect received a full neurorehabilitation program, including occupational therapy, physiotherapy, and neuropsychology. In one study (Lim et al. 2010), patients received behavioral therapy. In another study (Koch et al. 2012), patients were treated with 20 sessions of a 45 min therapy. Finally, two studies (Brighina et al. 2003; Bonni et al. 2013) added no rehabilitation therapy during the observation time.

8.5.4 Patient Characteristics

The time between acute brain damage and study inclusion varied considerably. Song et al. (2009), Koch et al. (2012), Cazzoli et al. (2012), and Kim et al. (2013) included patients in the acute/subacute stage, that is, within the first 3 months after brain damage. Patients with chronic neglect (i.e., more than 3 months after brain damage) were included in the studies by Brighina et al. (2003), Shindo et al. (2006), Kim et al. (2010), and Bonni et al. (2013). The remaining two studies included both patients in the subacute or in the chronic stage.

8.5.5 Follow-Up

The follow-up time after the stimulation ranged from 3 days (Nyffeler et al. 2009), 2 weeks (Brighina et al. 2003; Song et al. 2009; Koch et al. 2012; Bonni et al. 2013), 3 weeks (Cazzoli et al. 2012), to 6 weeks (Shindo et al. 2006). No information is reported concerning a potential fade-out of the stimulation effects. In all studies, the follow-up of the patients was 100 %.

8.5.6 Effect Sizes

The calculated effect sizes showed a high variability and ranged between small ($r=0.10$, $d=0.20$) and large effects ($r>0.50$, $d>0.80$). The largest effect sizes were found in the studies by Lim et al. (2010) and Cazzoli et al. (2012). Medium to large effect sizes were found in the studies by Nyffeler et al. (2009), Song et al. (2009), Koch et al. (2012), and Kim et al. (2010). Finally, small effect sizes were found in the study by Kim et al. (2013).

8.6 Discussion

All the ten identified studies, using rTMS in visual hemineglect treatment, applied inhibitory rTMS protocols (low-frequency stimulation or cTBS) and stimulated the contralesional parietal cortex. Two studies also included a condition in which the ipsilesional parietal cortex was stimulated using a high-frequency, excitatory rTMS protocol. Nine studies showed a significant improvement after inhibitory stimulation of the contralesional parietal cortex; one study found a significant improvement only after ipsilesional excitatory stimulation.

The studies show a considerable heterogeneity concerning design and quality. One study (Cazzoli et al. 2012) fulfilled CEBM level 1b and three studies level 2b (Song et al. 2009; Koch et al. 2012; Kim et al. 2013). Four studies were not sham controlled, and four studies evaluated only immediate effects after stimulation, without follow-up measurements. The remaining six studies had follow-up examinations up to 6 weeks. The number of patients included in the studies varied between 1 and 27. Only three studies (Shindo et al. 2006; Cazzoli et al. 2012; Kim et al. 2013) evaluated – in addition to neuropsychological testing – the activities of daily living (ADL) using the Catherine Bergego Scale (Azouvi et al. 2006) or the Barthel Index (Mahoney and Barthel 1965). Shindo et al. (2006) used a 0.9 Hz inhibitory protocol with contralesional application and found no change in the Barthel Index after stimulation. Cazzoli et al. (2012) used the Catherine Bergego Scale and found a significant improvement after contralesional continuous theta burst stimulation, but not after sham stimulation. Kim et al. (2013) evaluated both Barthel Index and Catherine Bergego Scale but found only a significant improvement in the Barthel Index for both low-frequency (1 Hz, ipsilesional) stimulation and high-frequency (10 Hz, contralesional) stimulation. All studies used batteries of different neuropsychological tests or test batteries specifically developed for neglect assessment (such as the behavioral inattention test, BIT). The effect of the stimulation was often different across outcome variables. One explanation may be methodological, since eight out of the ten rTMS studies used a focal figure-of-eight coil. Visual hemineglect is associated with multiple lesion sites (e.g., Verdon et al. 2010; Corbetta and Shulman 2011), and a focal stimulation may not be sufficient to influence all aspects tapped by a neuropsychological test battery. It is noteworthy that Cazzoli et al. (2012), who used a non-focal, round coil, found significant improvements in all tests. An example of the cTBS effect on visual exploration is shown in Fig. 8.2.

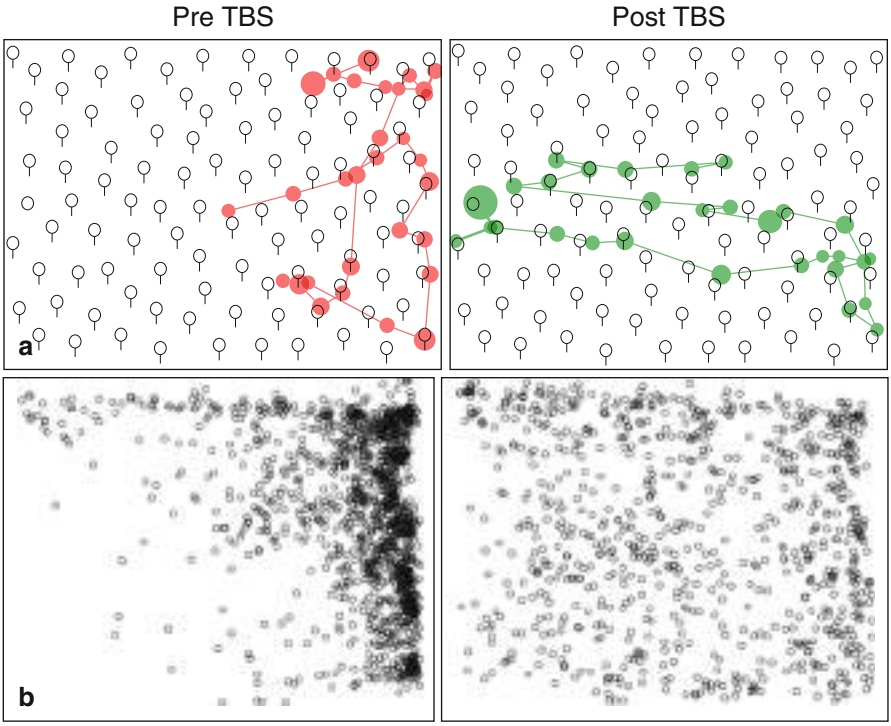

Fig. 8.2 Example of treatment effect with TBS on visual exploration in a search task (own unpublished data). (**a**) *Left side* visual exploration of a patient before TBS treatment. Eye movements (*filled circles*: fixations, lines saccades) were co-registered during the search task. The patient was instructed to search an array of stylized balloons (*circles with adjacent vertical lines*, representing the string), in order to locate one single balloon that was not connected to a string (i.e., a simple circle). In the pre-TBS condition, exploration is restricted to the *right side*; the target was not found on the *left side*. Post TBS (*right side*), the patient is able to find the target. (**b**) Overlay of fixation distributions of several trials. In the precondition, fixations were displaced to the *right side*. After TBS therapy, the exploration distribution was more balanced between left and right hemifield. *Open circles* represent fixations

Thus, high focal precision of stimulation may not be a primary goal for therapeutic rTMS application.

Inhibitory stimulation protocols were used in six studies, with low frequencies between 0.5 and 1 Hz. Four studies used inhibitory continuous theta burst stimulation. Two studies (Koch et al. 2012; Bonni et al. 2013) used the standard theta burst protocol described by Huang et al. (2011); two studies (Nyffeler et al. 2009; Cazzoli et al. 2012) used a modified protocol, described by Nyffeler et al. (2006).

The two protocols differ in the frequency within the bursts (50 Hz versus 30 Hz), in the total number of pulses (600 versus 801 pulses), and in the definition of the stimulation intensity (80 % active motor threshold versus 100 % resting motor threshold). Goldsworthy et al. (2012) directly compared the two protocols and

showed that their effect on MEP from the right first dorsal interosseous muscle was different. The standard protocol with 50 Hz bursts induced a neuroplastic response that was short lived and highly variable between subjects, whereas the modified protocol with 30 Hz bursts induced a lasting change in MEP amplitude that was consistent between subjects.

A lasting and consistent effect of cTBS between subjects is an advantage for the therapeutic application of TMS. Furthermore, the fact that the repeated cTBS application at the same day can disproportionately prolong its effects (Nyffeler et al. 2009) is an additional advantage.

From a clinical point of view, an optimal stimulation protocol for therapeutic interventions should present the following three properties: (1) easy application, (2) short application time, and (3) consistent therapeutic effects. An easy application means that no additional examinations such as neuroimaging or neuronavigation systems should be needed to localize the stimulation site. Indeed, only one study (Koch et al. 2012) used neuronavigation to localize the target site. The remaining studies localized the stimulation site by using the international 10–20 system, showing significant effects on visual hemineglect. Furthermore, the use of a non-focal coil may also increase the efficacy of the stimulation, as shown by Cazzoli and colleagues (2012).

A short application time of TMS is essential in a clinical setting. Protocols such as low-frequency stimulation ones, with daily applications over several weeks, are difficult to perform in a rehabilitation clinic and are often not well tolerated by patients. In contrast, cTBS application lasts about 40 s.

Furthermore, using the potential of a disproportionate prolongation of the effects by repeated cTBS application at the same day (see also Fig. 8.3), Cazzoli et al. (2012) could show that eight cTBS trains applied on 2 days have an ADL-relevant effect of up to 3 weeks. Finally, consistent therapeutic effects are important. Until today, there are no studies comparing head-to-head both TBS protocols in the therapy of visual hemineglect.

In conclusion, the present review on rTMS treatment of visual hemineglect shows an ongoing evolution from proof-of-concept studies to clinical application. However, the number of studies is limited. For best evidence, there is a clear advantage for the use of inhibitory rTMS protocols such as cTBS. At the moment, a week recommendation based on the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation; Guyatt et al. 2008) is given for cTBS protocols with repeated daily applications as described in the study of Cazzoli et al. 2012. This protocol has also a low burden for the patient due to the short application duration of the stimulation train and the duration of the whole therapy limited to 2 days. Furthermore, no serious side effects are reported in all studies using rTMS in visual hemineglect.

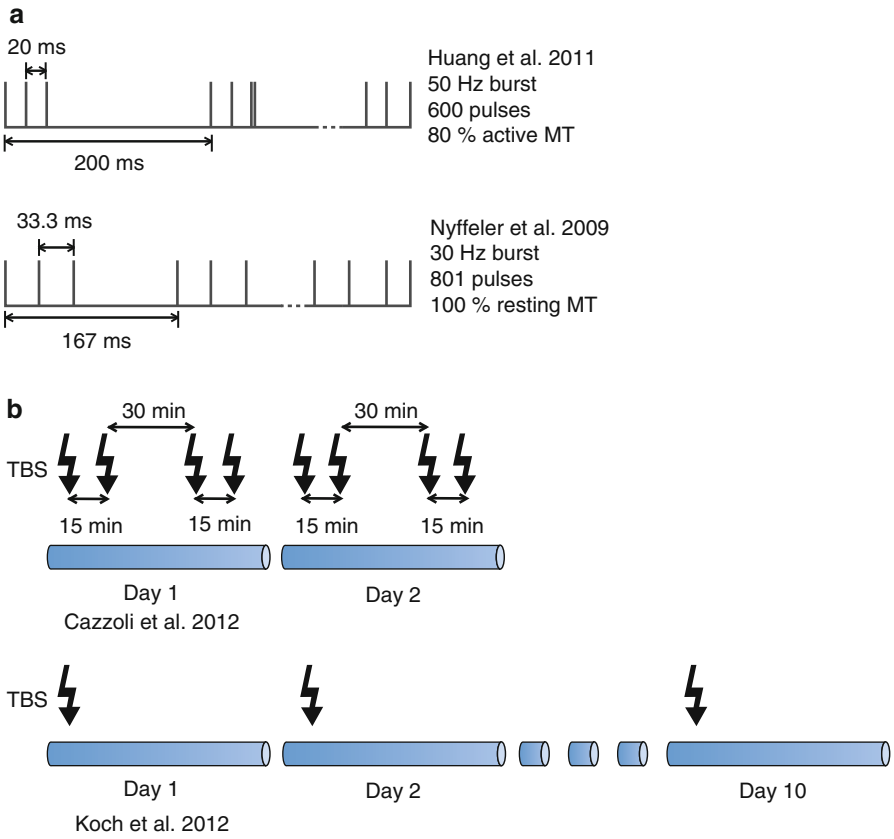

Fig. 8.3 (**a**) Parameters of the two cTBS protocols used in the treatment of visual hemineglect. *Above* the standard protocol according to Huang et al. (2011). *Below* the modified protocol according to Nyffeler et al. (2009). (**b**) Two types of treatment protocols by cTBS. *Above* the protocol used by Cazzoli et al. (2012) is based on the potentiation effect of repeated application of TBS on the same day. During 2 days, eight trains of TBS are applied. *Below* Koch et al. (2012) used a more classical approach (also used in many low-frequency protocols) with daily application of one train over 10 days

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Clinical Applications of rTMS in Parkinson's Disease

9

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Abstract

Parkinson's disease (PD) has wide-ranging clinical features, and repetitive transcranial magnetic stimulation (rTMS) therapy has been tried for many aspects of PD. Underlying mechanism of rTMS therapy in PD remains unclear, but several possibilities are proposed such as endogenous dopamine release or restoration of neural plasticity or network activity. Motor symptoms are a cardinal feature of PD, for which evidence suggested moderate efficacy of rTMS. High-frequency (HF) rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1 rTMS) or over the DLPFC, and low-frequency (LF) rTMS over the SMA were most favorable. Long-term administration of levodopa, a major agent for medical therapy of PD, can induce a motor complication called levodopa-induced dyskinesia (LID). Several types of rTMS were reported to be effective for the LID. rTMS has also been tried for non-pharmacological treatment of non-motor symptoms of PD including depression. A "weak recommendation" in favor of HF rTMS of the left DLPFC can be given for the treatment of depressive symptoms associated with PD. These are examples of growing application of rTMS therapy to PD for symptoms other than the classical motor symptoms. As such, rTMS has a potential to become an important adjunctive treatment for PD. Well-designed large clinical trials are needed to establish its utility in the clinical settings.

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9.1 Introduction

Parkinson's disease (PD) has wide-ranging signs and symptoms. It is classically characterized by motor symptoms such as bradykinesia, resting tremor, muscle rigidity, and postural instability (Gibb and Lees 1988); on the other hand, more recent reports have emphasized that various non-motor symptoms can also be a major problem (Chaudhuri et al. 2006). Dopamine depletion resulting from neuronal loss in the substantia nigra of the midbrain plays a crucial role in the motor symptoms, for which dopamine replacement therapy is effective. Prolonged treatment by dopaminergic medicine including levodopa, however, can cause motor complications such as wearing off or levodopa-induced dyskinesia (LID). In addition, dopamine replacement therapy is essentially ineffective for most of the non-motor symptoms. Based on such variation in the clinical presentation of PD, various pharmacological and non-pharmacological therapies have been tried, some of which are successful, such as the deep brain stimulation (Miocinovic et al. 2013). Noninvasive brain stimulation including repetitive transcranial magnetic stimulation (rTMS) can also be a non-pharmacological therapeutic option for PD.

In this chapter, we will pick up several aspects of PD where promising effects of rTMS therapy were reported. Mechanisms underlying clinical utility of rTMS in PD is still yet to be elucidated, but several hypotheses were proposed (Sect. 9.2). On the other hand, clinical studies have demonstrated moderate efficacy of cortical stimulation by rTMS on the motor symptoms (Sect. 9.3). rTMS therapy for the motor symptoms could well be an important adjunctive therapy supporting dopaminergic medication. This chapter will provide a brief overview of rTMS trials in terms of target brain sites and other stimulation parameters. Regarding motor complications (Sect. 9.4) and non-motor symptoms (Sect. 9.5), rTMS has a potential as a novel, key therapy, since these symptoms are sometimes resistant to conventional treatments.

rTMS in itself has few severe side effects, as long as exclusion criteria and dosage limitation for rTMS (Rossi et al. 2009) are strictly observed. A detailed review article has been published with regard to safety issues specific for PD (VonLoh et al. 2013). Researchers applying a brand-new stimulation paradigm should be fully aware of current safety guidelines.

9.2 Mechanisms of rTMS for PD Therapy

What can rTMS do to the dopaminergic system in the brain, a key circuit to treat PD? Dopaminergic cells are situated subcortically such as in the substantia nigra of the midbrain, although (r)TMS can only stimulate cortical neurons (for basic neurophysiology of rTMS, *see* Chap. 1). In this regard, a line of evidence from animal studies showed increased dopamine concentration in the rat striatum by cortical stimulation (Ben-Shachar et al. 1997; Keck et al. 2002). Furthermore, Kanno et al. explored stimulation intensity dependency of the dopamine increase (Kanno et al. 2004). A session of rTMS at approximately 110 % of the motor threshold induced

significant dopaminergic enhancement in the dorsal striatum. Interestingly, however, rTMS with lower or higher stimulus intensity did not modulate the dopamine level at all. This nonlinear stimulus intensity dependency should perhaps be taken into account to establish a novel stimulation protocol. In fact, positive results have been reported in clinical trials using stimulus intensity around the motor threshold (Elahi and Chen 2009).

Human as well as monkey studies with the positron emission tomography also suggested dopamine secretion in the striatum by rTMS (Strafella et al. 2003; Ohnishi et al. 2004), but patient studies so far are not very promising. In early PD patients with unilateral symptoms, rTMS over the primary motor cortex (M1) contralateral to the symptomatic side did decrease [^{11}C] raclopride-binding potential in the putamen, suggesting increased dopamine level in the putamen (Strafella et al. 2005). The amount of the decrease, however, was significantly less than that induced by rTMS over the other primary motor cortex. Thus, it could be the case that the severer degeneration of the dopaminergic system was, the less dopamine increase rTMS could bring about.

Alteration in the neural plasticity or excitability under abnormal dopaminergic function might be restored by rTMS. When applied over the human M1, rTMS is shown to induce excitability change lasting minutes to hours. It is generally assumed that high-frequency (HF; 5 Hz or higher) rTMS increases (Pascual-Leone et al. 1994b; Peinemann et al. 2004), and low-frequency (LF; 1 Hz or lower) rTMS decreases (Chen et al. 1997; Romero et al. 2002) the excitability of the M1. Later researches showed that the rTMS-induced excitability change had several key features in common with synaptic plasticity such as long-term potentiation (LTP) or depression (LTD). In PD, various types of altered neural plasticity has been reported, some of which were related to behavioral dysfunctions. However, meaning of altered plasticity-like effect as indexed by motor cortical excitability change in the behavioral context remains to be investigated. Importantly, clinical benefit does not always go parallel with changes in physiological markers (Koch 2013).

Cellular and molecular mechanism underlying rTMS therapy has been proposed in several animal studies. A research demonstrated that rTMS therapy to 6-hydroxydopamine (OHDA) induced parkinsonian rat improved the motor symptoms and was associated with lower level of tumor necrosis factor-alpha and cyclooxygenase-2 (Yang et al. 2010). The authors discussed that rTMS can improve the motor symptoms by inhibiting inflammatory process. A later study, also conducted on a rat model of PD by 6-OHDA, reported increased expression of various neurotrophic and growth factors (Lee et al. 2013). Interestingly both studies reported that dopaminergic cell loss can be prevented by multiple sessions of rTMS.

9.3 rTMS Therapy for Motor Symptoms of PD

After the first attempt to apply HF rTMS to PD patients (Pascual-Leone et al. 1994a), quite a few clinical studies have been performed to investigate clinical effects of rTMS on motor symptoms in PD patients. Motor symptoms are the key

features of PD, for which the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al. 1987) part III has been accepted as a measure in clinical trials. There are two meta-analyses on rTMS therapy for the motor symptoms of PD, using the UPDRS part III as the outcome measure (Fregni et al. 2005; Elahi and Chen 2009). In the first meta-analysis (Fregni et al. 2005), 224 patients were pooled from 12 citations, whose mean (standard deviation, SD) Hoehn and Yahr stage was 2.4 (0.8). Stimulation protocols, such as target brain sites, stimulation frequency, stimulation intensity, total number of pulses, and number of sessions, were quite variable. The authors revealed an overall favorable effect from the pooled results of 8 controlled studies: the pooled effect size (95 % confidence interval, 95 % CI) was 0.60 (0.24, 0.96) based on the random effect model. Assessment took place immediately after the treatment. They argued against a possible publication bias based on results of the funnel plot. The issue of stimulation frequency was further investigated in the second meta-analysis, where studies using HF and LF rTMS were analyzed separately (Elahi and Chen 2009). In total 275 patients were included from 10 studies, whose baseline Hoehn and Yahr stages were between 1 and 4. The result showed efficacy of HF rTMS: the pooled mean effect size (95 % CI) was 0.58 (0.27, 0.90), in favor of rTMS, whereas effects of LF rTMS were too variable to draw any firm conclusion. Influence of other stimulation parameters including target brain site or stimulation intensity still remains to be elucidated. Some results are summarized in the Table 9.1 for blinded randomized controlled studies published after these two meta-analyses.

In this section, we try to characterize the results of clinical trials according to target brain regions. A target site would be the first parameter we have to take into account. Neuroimaging studies have revealed several cortical areas whose activities were different in PD patients from those in healthy people. Although it is generally assumed that cortical activity is decreased under dopaminergic neuron degeneration (Alexander et al. 1986; DeLong and Wichmann 2007), different patterns of brain activation were reported (Playford et al. 1992; Jenkins et al. 1992; Rascol et al. 1992; Sabatini et al. 2000; Yu et al. 2007; Tessa et al. 2010). The M1 and prefrontal cortex have been two common target sites, and studies on other premotor areas were also published.

9.3.1 rTMS over the Primary Motor Cortex (M1)

The M1 has been the most common target site in rTMS therapy for the motor symptoms of PD. It is not severely damaged in PD from the pathological point of view, but plays an important role in motor symptoms in PD via dense connection with other motor-related cortical and subcortical areas. A classical model for the pathophysiology of PD postulated decreased activity in the motor thalamus and resulting hypoactivation in the cerebral cortex including the M1 (Alexander et al. 1986; DeLong and Wichmann 2007). Some neuroimaging studies supported this notion by showing decreased activity in the M1 (Rascol et al. 1992; Buhmann et al. 2003; Tessa et al. 2010), whereas others demonstrated hyperactivity in the M1 (Haslinger

Table 9.1 A summary of blinded randomized controlled trials

Reference	Population[a]	Interventions	Main results
Cardoso et al. (2008)	21 PD patients with depression (1) rTMS group ($N=11$): 67 (8.3) years old, 11 (7.6) years duration, Hoehn and Yahr stage 2.54 (0.82) (2) Fluoxetine group ($N=10$): 63 (7.1) years old, 11 (6.4) years duration, Yahr 2.50 (0.53)	(1) DLPFC rTMS with placebo: 50 trains of 15 s duration at 120 % MT and 5 Hz frequency (3750 pulses) (2) Sham rTMS with fluoxetine (20 mg/day) Three sessions per week for 4 weeks (12 sessions in total)	No improvement in the UPDRS BDI and HRSD improved in both groups
Hamada et al. (2008)	88 PD patients (1) SMA group ($N=55$): 65.3 (8.9) years old, 8.1 (4.2) years duration, Hoehn and Yahr stage 2–4 (2) Sham group ($N=43$): 67.4 (8.5) years old, 7.8 (6.7) years duration, Hoehn and Yahr stage 2–4	(1) SMA rTMS: 20 trains of 10 s duration with 50 s intervals at 5 Hz and 110 % AMT for a leg muscle (1000 pulses) (2) Sham rTMS 8 times weekly	Significant improvement in the UPDRS part III at least up to 12 weeks
Filipović et al. (2009)	10 PD patients with dyskinesia, a crossover study with a minimum of 2-week interval. 64.5 (9.5) years old, 15.6 (5.7) years duration	(1) Real rTMS: 3 series of 600 stimuli at just below AMT and 1 Hz frequency with 1 min intervals (2) Sham rTMS 4 consecutive days	Significant improvement of dyskinesia on the next day of the last stimulation from the baseline only in the real rTMS group
Koch et al. (2009)	20 PD patients with dyskinesia 64.7 (6.9) years old, 10.4 (4.3) years duration	(1) Cerebellar cTBS: 2 trains of 40 s cTBS (600 pulses each) with a 2 min interval at 80 % AMT (2) Sham cTBS 10 sessions (5 sessions per week)	Improvement in the dyskinesia up to 4 weeks
Filipović et al. (2010)	10 PD patients with dyskinesia, a crossover study with a minimum of 2-week interval. 64.5 (9.5) years old, 15.6 (5.7) years duration Hoehn and Yahr stage 3.3 (0.67)	(1) Real rTMS: 3 series of 600 stimuli at just below AMT and 1 Hz frequency with 1 min intervals (1800 pulses) (2) Sham rTMS 4 consecutive days	No improvement in the UPDRS part III assessed in the "off" state

(continued)

Table 9.1 (continued)

Reference	Population[a]	Interventions	Main results
Pal et al. (2010)	22 PD patients with depression (1) Actively treated group ($N=12$): 68.5 years old, 6.0 years duration (2) Sham group ($N=10$): 67.5 years old, 6.5 years duration	(1) Left DLPFC rTMS: 12 trains of 10 s duration with 20 s intervals (600 pulses) at 90 % RMT and 5Hz frequency (2) Sham rTMS 10 sessions	Significant improvement of depression 30 days after treatment Trend-wise improvement in UPDRS part III
Benninger et al. (2011)	26 PD patients. (1) iTBS group ($N=13$): 62.1 (6.9) years old, 10.8 (7.1) years duration, Yahr 2.6 (0.2) (2) Sham group ($N=13$): 65.6 (9.0) years old, 6.5 (3.4) years duration, Yahr 2.5 (0.1)	(1) iTBS over the M1 and DLPFC with a circular coil (2) Sham TBS 8 sessions (2 weeks, a daily session for 4 consecutive days/week)	No effects on the UPDRS-III Improvement in the mood
Benninger et al. (2012)	26 PD patients (1) 50 Hz group ($N=13$): 64.5 (9.1) years old, 8.6 (4.1) years duration, Yahr 2.4 (0.2) (2) Sham group ($N=13$): 63.7 (8.3) years old, 9.3 (6.8) years duration, Yahr 2.5 (0.3)	(1) 50 Hz rTMS: 6 s duration rTMS with a circular coil at 80 % AMT and 50 Hz frequency to both M1s (300 pulses each) (2) Sham rTMS 8 sessions (4 consecutive days/week)	No improvement in motor symptoms
Shirota et al. (2013)	106 PD patients (1) 1 Hz SMA ($N=36$): 68.8 (7.6) years old, 8.5 (7.3) years duration, Yahr 2–4 (2) 10 Hz SMA ($N=34$): 67.9 (8.4) years old, 7.8 (6.6) years duration, Yahr 2–4 (3) Sham rTMS ($N=36$): 65.7 (8.5) years old, 7.6 (4.4) years duration, Yahr 2–4	(1) 1 Hz SMA: a single session at 1 Hz (1000 pulses) (2) 10 Hz SMA: 20 trains of 5 s duration at 10 Hz (1000 pulses) (3) Sham rTMS Stimulus intensity: 110 % AMT for a leg muscle (if this was higher than 110 % RMT for a hand muscle, the latter was chosen) 8 sessions weekly	Improvement in the UPDRS-III lasted up to 20 weeks in 1 Hz group. Improvement in 10 Hz and sham returned to the baseline after treatment

HRSD Hamilton rating scale for depression, *BDI* Beck depression inventory, *AMT* active motor threshold, *MT* motor threshold

[a]Age, disease duration, and Hoehn and Yahr stage are presented as mean (standard deviation), whenever possible

et al. 2001; Eckert et al. 2006; Yu et al. 2007). As mentioned in Sect. 9.2, rTMS over the M1 is supposed to be able to increase or decrease the excitability of the M1, dependent on the stimulation frequency; both types of rTMS have been thus tried.

Animal studies also supported potential efficacy of M1 stimulation. HF electrical stimulation of the M1 was effective in the nonhuman primate model (Drouot et al. 2004). In rodent studies it is often difficult to stimulate a specific brain area by rTMS, but Gradinaru et al. elegantly demonstrated that depolarization of the motor cortex can be a good treatment option for PD (Gradinaru et al. 2009). They reported that selective HF depolarization of the layer V pyramidal neurons in the M1 had similar behavioral effects as artificial electric stimulation of the subthalamic nucleus, which is one of the major targets of the deep brain stimulation. These results suggest that long-lasting electrophysiological change in the M1 can ameliorate the motor symptoms of PD.

It is difficult to draw a firm conclusion from the results of currently available clinical trials mainly because of variable stimulation protocols and small number of participants in each trial. Several studies with HF rTMS reported improvement in the UPDRS motor score (Siebner et al. 2000; Khedr et al. 2003; Lefaucheur et al. 2004), whereas some others reported no clinical benefit (Rothkegel et al. 2009; Benninger et al. 2012). Variation in stimulus parameters among studies (e.g., some used 5 Hz, others used 10 Hz) defies any generalization, and total number of patients studied is very small. On the other hand, most of LF rTMS over the M1 failed to show positive effects (Okabe et al. 2003; Rothkegel et al. 2009; Filipović et al. 2010), with some exception (Lefaucheur et al. 2004). Compared with stimulus frequency, dimension of stimulus intensity is less explored. Regardless of frequency, higher intensity such as 120 % of resting motor threshold tended to be effective (Sommer et al. 2002; Khedr et al. 2003), but positive results were also reported in two studies using stimulus intensity as low as 80 % of it (Lefaucheur et al. 2004; González-García et al. 2011). Mally et al. investigated impact of stimulus intensity using 1 Hz rTMS and found a nonlinear relationship: rTMS with 0.57 tesla had significant effect, whereas that with higher (0.80 tesla) or lower (0.34 tesla) intensity did not improve the motor function (Mally and Stone 1999). When targeting the "M1" focally with TMS, there can be several possibilities: right and left M1 for a hand representation and leg M1. Whereas most studies stimulated uni- or bilateral hand M1, Khedr et al. combined all of the three and reported good efficacy (Khedr et al. 2003, 2006, 2007). Lastly, temporal distributions of rTMS sessions can also be pointed out as an important factor. Some studies used single, whereas others multiple, rTMS sessions. Among studies on multiple rTMS sessions, most applied daily rTMS sessions 4–10 times for 1 or 2 weeks, with some exception, e.g., weekly rTMS 8 times (Okabe et al. 2003). Accordingly the follow-up period is variable, too. In general multiple rTMS sessions are favorable, but this is not always the case. In this regard, two LF rTMS studies are contradictory. Lefaucheur et al. reported effect of a single rTMS session (Lefaucheur et al. 2004); on the contrary Okabe et al. reported no improvement with weekly rTMS sessions compared with sham rTMS (Okabe et al. 2003).

In addition to "conventional" rTMS described above (e.g., 1 Hz rTMS or 5 Hz rTMS), so-called "patterned" rTMS has been introduced more recently. Among several patterned rTMS protocols, theta-burst stimulation (TBS) is most widely studied (Huang et al. 2005). A TBS session requires less time than conventional rTMS, nevertheless seems as effective (Zafar et al. 2008). Most of clinical studies, however, were not as promising (Rothkegel et al. 2009; Benninger et al. 2011; Degardin et al. 2012). A single session of intermittent TBS (iTBS, supposed to induce LTP-like plasticity) improved bradykinesia and rigidity mildly (Degardin et al. 2012), but no efficacy was shown in the UPDRS in a randomized, double-blind, sham-controlled study (Benninger et al. 2011). The negative findings can be partly attributed to altered response to rTMS in PD. Studies investigating plasticity induction in PD patients in general reported ineffectiveness or responses different from healthy populations (Eggers et al. 2010; Suppa et al. 2011; Kishore et al. 2012a). A recent study even demonstrated that responses to TBS are highly variable in the healthy population (Hamada et al. 2013).

Indeed, at least two other factors should be taken into account for explaining the variable effects of rTMS in PD: medication and aging. First, aftereffect of brain stimulation is influenced by simultaneous administration of central nervous system-acting drugs. Especially, levodopa, which is very often administered to PD patients requiring additional therapy such as rTMS, has been found to affect several noninvasive brain stimulation protocols in a dose-dependent manner (Monte-Silva et al. 2010; Thirugnanasambandam et al. 2011). Second, effects of rTMS have been mainly demonstrated and investigated in healthy young participants; some more recent researches, however, elucidated age-related decline in the effect of rTMS (Müller-Dahlhaus et al. 2008; Fathi et al. 2010; Bashir et al. 2014). It can be the case that older patients taking medications such as levodopa do not respond to an rTMS protocol as expected in a younger healthy population.

9.3.2 rTMS over the Prefrontal Cortex

The second often investigated brain site is the dorsolateral prefrontal cortex (DLPFC). Clinical trials using DLPFC rTMS most commonly targeted PD patients with depression (Sect. 9.5), but influence on the motor function is reported as well. HF rTMS was most often applied over the left DLPFC. An open study demonstrated significant improvement in the UPDRS part III score (Epstein et al. 2007). Pal et al. reported a large amount of improvement in the UPDRS motor score (7.5 points) in a randomized double-blind study, but it did not reach a statistically significant level (Pal et al. 2010). Other studies did not find significant effect of DLPFC rTMS on the motor symptoms (Fregni et al. 2004; Boggio et al. 2005). It is still more controversial whether rTMS over the DLPFC can improve motor symptoms of PD without depression (Dias et al. 2006; del Olmo et al. 2007). There may be difficulty to discriminate mood-related motor improvement and "true" improvement of motor function; rTMS over the DLPFC, however, would be very efficient if it can ameliorate both motor and non-motor functions. More recently, an open-label study reported

effectiveness of prefrontal rTMS (Spagnolo et al. 2014). The authors targeted both the M1 and bilateral prefrontal regions with "deep" rTMS at 10 Hz frequency using a specialized stimulation coil termed H-coil. Twelve sessions over 4 weeks yielded positive effect. Further controlled studies are needed for this new technique.

9.3.3 rTMS over Other Frontal Areas

Between the M1 and the DLPFC lie so-called secondary motor areas such as the supplementary motor area (SMA) and the dorsal premotor cortex (PMd), which have not attracted much interest as target sites for rTMS therapy in PD. A common assumption here is deactivation of the SMA (Playford et al. 1992; Jenkins et al. 1992; Rascol et al. 1992; Buhmann et al. 2003) and hyperactivity in the PMd (Samuel et al. 1997; Sabatini et al. 2000). Therefore, a study by Boylan et al. was surprising in that an HF (10 Hz) rTMS over the SMA, which was supposed to increase SMA activity, worsened motor function (Boylan et al. 2001). A clue might exist in a study on a healthy population where worsening of a motor behavior was induced by HF rTMS over the SMA (Gerloff et al. 1997). Behavioral effects of rTMS might be different from physiological effects. Furthermore, the role of SMA in PD is somewhat complex. The hypoactivation has been reported during a cued simple motor task; on the other hand, hyperactivity of the anterior SMA during a complex motor task (Catalan et al. 1999) or self-initiated movement (Eckert et al. 2006) has been reported. One study revealed deep brain stimulation-induced reduction of SMA activity paralleled with learning efficiency, discussing a potential role of overactive SMA-subthalamic nucleus network in PD (Mure et al. 2012). These complicated results might be a reason why not so many researchers were lured by SMA rTMS as a therapy for PD.

Two multicenter clinical trials from Japan have revealed significant improvement of the motor symptoms in PD compared with sham stimulation. In the first trial, 5 Hz rTMS over the SMA was delivered in 99 PD patients (Hamada et al. 2008, 2009). An rTMS session with 1000 pulses was repeated 8 times weekly. Stimulus intensity was set at 110 % AMT for a leg muscle. The real rTMS group showed approximately 4-point improvement in the UPDRS part III, in contrast with almost no change in the sham group. The later study explored stimulus frequency dependency of the SMA rTMS using similar parameters (Shirota et al. 2013). In total 106 patients were randomly assigned to 10 Hz rTMS, 1 Hz rTMS, or the sham stimulation groups. Contrary to evidence from M1 rTMS, it was the 1 Hz (i.e., LF) rTMS that improved the motor symptoms best; improvement in the 10 Hz rTMS group was not significantly different from that in the sham group. The beneficial effect of the 1 Hz rTMS lasted at least 12 weeks after the end of the treatment. In future studies, it would be more fruitful to try rTMS with 5 Hz or slower stimulus frequency when targeting the SMA. Both effects of 5 and 1 Hz rTMS should be replicated in another independent clinical trial to establish their efficacy.

Regarding the PMd, we can find only several open-label studies with a small sample size. Buhman et al. applied 1200 pulses of 1 Hz rTMS over the PMd at 80 %

AMT and reported significant improvement in the UPDRS of mild to moderate PD patients (Buhmann et al. 2004). On the other hand, the same rTMS paradigm did not improve motor functions of more advanced patients (Bäumer et al. 2009). High-frequency, 5 Hz rTMS was reported to be ineffective for clinical symptoms (Mir et al. 2005).

9.3.4 Short Conclusions

Taken together, it is likely that rTMS is moderately effective for motor symptoms of PD, but that several issues need to be clarified. Stimulation parameters, such as a target region, stimulation frequency, and stimulation intensity, and stimulation schedule (e.g., daily, weekly) should be refined further. So far the evidence suggests that HF rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1) or DLPFC with 6–12 sessions, and LF (1 Hz) rTMS of the SMA with a weekly schedule for 8 weeks were most favorable for the treatment of motor symptoms in PD. There are responders and nonresponders for a certain rTMS protocol even in healthy, relatively young people (Hamada et al. 2013). Considering the great variability in the clinical presentation of PD including age, disease duration, prominent symptom, and medication, some strategy to find out responders may be needed, or stimulation protocol should be adjusted to each patient. Further, larger controlled studies are also needed to establish the therapeutic effect of rTMS on the motor symptoms.

Given the variability of methods used and of the results across trials, "no (firm) recommendation" (Guyatt et al. 2008) can be given in favor of rTMS therapy for motor symptoms of PD.

9.4 Levodopa-Induced Dyskinesia (LID)

Long-term levodopa therapy often poses a problem called motor complications including LID. In a prospective study, its incidence was reported as high as 45 % of PD patients treated with levodopa for years (Rascol et al. 2000). If a patient develops LID, physicians may be more or less reluctant to increase dopaminergic medication (Fabbrini et al. 2007; Rascol et al. 2000), resulting in suboptimal treatment. Therefore, importance of seeking treatments for the LID may be twofold: decrease of LID can in itself improve the quality of life (QOL) and allow the dopaminergic treatment at a more desirable level.

A line of evidence has shown a pivotal role of abnormal synaptic plasticity in the LID; the plasticity-like effect induced by rTMS may therefore be a good treatment option. Dopamine depletion first abolishes plastic changes at the corticostriatal synapses. The LTP, however, can be restored following chronic dopamine substitution. Intriguingly, this synaptic potentiation could be reversed in PD rats without the LID by low-frequency stimuli which usually cause LTD in a "neutral" synapse, whereas presence of LID was closely associated with loss of this "de-potentiation," showing

overactivity of the synapses (Picconi et al. 2003). Evidence from the human M1 has also elucidated several types of altered plasticity-like effect in PD patients with LID (Huang et al. 2011; Kishore et al. 2012b; Morgante et al. 2006). Clinically, the overactivity of the corticostriatal synapses might be related to excess of abnormal involuntary movements in the LID, and reducing it might be a potential target for treatment of the LID.

Several clinical trials of rTMS therapy for the LID targeted frontal brain areas based on human neuroimaging studies demonstrating altered, mainly hyperactive, brain function in PD with LID (Rascol et al. 1998). Koch et al. for the first time demonstrated influence of single-session SMA rTMS on the LID. In compatible with the notion of cortical hyperactivity, 1 Hz rTMS, supposed to decrease the activity of the SMA, reduced the LID, whereas 5 Hz, presumably "excitatory," rTMS induced trend-wise worsening (Koch et al. 2005). A following research from the same group, however, revealed that the effect did not have a cumulative effect with 5 daily sessions (Brusa et al. 2006). A more recent 10-day rTMS trial also reported short-lasting beneficial effect of low-frequency rTMS over the SMA (Sayin et al. 2014). Another strategy would be to decrease activity in the M1, but researches have shown only transient or mild effect of M1 rTMS (Wagle-Shukla et al. 2007; Filipović et al. 2009).

Cerebellar TBS was introduced by Koch et al. as a treatment option for the LID, which seems to have the best efficacy so far (Koch et al. 2009). A 10-day course of the cTBS sessions (5 days a week for 2 weeks) improved the LID compared with a sham cTBS course for at least 4 weeks. Further investigations are warranted on this protocol.

While some of the reports mentioned are encouraging, so far "no recommendation" (Guyatt et al. 2008) can be given in favor of rTMS therapy for LID in PD in routine clinical practice.

9.5 Non-motor Functions

More and more attentions have been paid to non-motor symptoms of PD. Some researchers reported that the non-motor symptoms affect the QOL more than the motor symptoms and that they are very often overlooked (Chaudhuri et al. 2010; Zesiewicz et al. 2010). Most of them do not respond to dopaminergic therapies. The non-motor symptoms of PD include neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal symptoms, and sensory symptoms (Chaudhuri et al. 2006).

Among the non-motor symptoms of PD, depression is currently the best responding symptom to rTMS. The strategy is closely related to rTMS therapy for major depression in the field of psychiatry. High-frequency rTMS over the left DLPFC and low-frequency rTMS over the right DLPFC are two major options (Padberg and George 2009), and high-frequency rTMS has been mainly tried in PD patients. In a relatively large sham-controlled study on 42 PD patients with depression, influence of 10 sessions HF (15 Hz) rTMS of the left DLPFC on depression was comparable with that of the selective serotonin reuptake inhibitor

fluoxetine, while rTMS was associated with less side effects and greater motor and cognitive improvement (Fregni et al. 2004). High-frequency rTMS can improve the mood in PD without any apparent side effects in other cognitive domains (Boggio et al. 2005). A more recent study reported differential influence of rTMS and an antidepressant on regional brain activity using fMRI, which suggests potential add-on effects of rTMS combined with antidepressants (Cardoso et al. 2008). A subsequent double-blind sham-controlled study further confirmed significant improvement of depression as well as trend-wise effect on motor function (Pal et al. 2010). Ten sessions of 5 Hz rTMS over the left DLPFC led to a considerable improvement on depression rate scales as well as motor scores 30 days after treatment ended.

The data from the two larger controlled clinical trials warrant a "weak recommendation" (Guyatt et al. 2008) in favor of HF rTMS of the left DLPFC in the treatment of depressive symptoms associated with PD.

9.6 Summary and Future Directions

Treatment of PD requires a multidisciplinary approach in which rTMS can be involved. We need, however, further research, especially large-scale clinical studies, to establish clinically meaningful utility of rTMS therapy.

For motor symptoms, we can find several well-designed clinical trials, but their overall efficacy is only moderate. HF rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1 rTMS) or over the DLPFC, and LF rTMS over the SMA were most favorable so far. Since motor symptoms of PD can be successfully treated by dopaminergic medications in many cases, more benefit is needed for the rTMS therapy to be a major therapeutic option.

Positive results that need further elaboration and confirmation were also reported in relatively small studies for some of the motor complications such as LID.

An evidence-based "weak recommendation" (Guyatt et al. 2008) in favor of HF rTMS of the left DLPFC can be given for the treatment of depressive symptoms associated with PD.

In each of the domains, further evidence is required in larger studies. Several factors, including, but not limited to, aging of the brain, variation in clinical presentation, or influence of medication, should be taken into account in investigating newer stimulation paradigm. Basic understanding of mechanisms of rTMS would be another prerequisite for future successful clinical trials.

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rTMS in the Treatment of Neuropathic Pain

10

Jean-Pascal Lefaucheur

Abstract

Motor cortex stimulation (MCS) using surgically implanted epidural electrodes was shown to produce pain relief in patients with chronic neuropathic pain. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive approach that could be used as a preoperative tool to predict MCS outcome and also could serve as a therapeutic procedure in itself to treat pain disorders. This therapeutic application requires repeated rTMS sessions every day for 1 or 2 weeks, followed by a maintenance protocol. The most studied cortical target is the precentral cortex, but other targets, especially the dorsolateral prefrontal cortex, could be of interest. The analgesic effects of cortical stimulation relate to the activation of various circuits modulating neural activities in remote structures, such as the thalamus, the limbic cortex, the insula, or descending inhibitory controls. Motor cortex rTMS as a therapeutic option in patients with neuropathic pain is supported by various sets of results with a high level of evidence statistically, but whose significance remains to be proven clinically. Also, the procedure needs to be further optimized before being fully integrated into clinical practice.

10.1 Introduction

Neuropathic pain is a major public health problem because of its prevalence (affecting up to 6–7 % of the general population (Bouhassira et al. 2008)) and because of the limited efficacy of current therapies: only 30–40 % of patients declare they receive satisfactory relief from their chronic pain through pharmacological treatment (Attal et al. 2006). In contrast to all the other clinical conditions concerned by

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noninvasive cortical stimulation therapy, neuropathic pain was first treated in the early 1990s by invasive motor cortex stimulation (MCS) using surgically implanted electrodes (Tsubokawa et al. 1991a, b). When repetitive transcranial magnetic stimulation (rTMS) became available, it was tempting to determine whether rTMS could also produce significant analgesic effects. We first observed such effects by applying rTMS trains at 10 Hz over the motor cortex in a small series of patients with chronic neuropathic pain (Lefaucheur et al. 1998). Since this preliminary report, numerous studies have confirmed the value of rTMS to relieve various types of pain, either chronic ongoing pain or experimentally provoked pain (Mylius et al. 2012). At present, there is a high level of evidence in favor of a real analgesic effect of high-frequency rTMS on focal neuropathic pain when rTMS is applied on the primary motor cortex (M1) contralateral to pain location (Lefaucheur et al. 2014). In this chapter, we will focus on the use of rTMS in neuropathic pain.

10.2 Analgesic Effects of Motor Cortex rTMS

To date, many studies have been performed to test the ability of rTMS to produce analgesic effects in patients with chronic pain syndrome. Various reviews and meta-analyses can be found on this topic (Lefaucheur 2008b; Lefaucheur et al. 2008a; Leung et al. 2009; O'Connell et al. 2010). Most studies have been performed in patients with neuropathic pain, using the contralateral M1 area as the stimulation target.

First, Migita et al. (1995) delivered 200 TMS pulses at 0.2 Hz using a nonfocal, circular coil centered over the motor cortex, contralateral to the painful side, in two patients with central pain. The first patient experienced 30 % pain relief for 1 h, whereas TMS was ineffective for the second patient. TMS effects paralleled the outcome of subsequent MCS implantation. Canavero et al. (2003) applied a similar protocol of repeated single-pulse TMS in a series of patients with chronic pain secondary to stroke or spinal cord lesion. The procedure consisted of two trains of 100 stimuli delivered at 0.2 Hz over the motor cortex using a figure-of-eight coil for arm stimulation or a double-cone coil for leg stimulation. From the nine patients enrolled in this placebo-controlled study, one patient was relieved for allodynia and four patients for both spontaneous pain and allodynia. Pain relief lasted 16 h in one case.

These two studies were based on a very low frequency of stimulation with single-pulse TMS (0.2 Hz), compared with the frequencies used in chronic implanted MCS that range from 20 to 55 Hz (Nguyen et al. 2003, 2009). Frequency is considered as one of the most crucial parameters of stimulation, conditioning the functional result of rTMS despite high interindividual variability. High-frequency stimulation (>5 Hz) is able to excite the underlying motor cortex for a few minutes (Pascual-Leone et al. 1994), while low-frequency stimulation (<5 Hz) is rather inhibitory (Chen et al. 1997). In our first placebo-controlled study, rTMS was applied to the motor cortex at high (10 Hz) or low (0.5 Hz) frequency, in a series of 18 patients with chronic pain secondary to thalamic stroke, brain stem lesion, or brachial plexus lesion (Lefaucheur et al. 2001a). We found that rTMS administered

at 10 Hz, but not at 0.5 Hz, resulted in pain relief, regardless of the side of the stimulated hemisphere (Lefaucheur et al. 2001a). This was the first demonstration of the ability of high-frequency motor cortex rTMS to relieve chronic neuropathic pain of peripheral or central origin. A second group showed that rTMS provided better alleviation of pain at 20 Hz than at 1 Hz (André-Obadia et al. 2006). A third group found that 10 Hz rTMS was more efficacious than 5 Hz rTMS, while 1 Hz rTMS did not produce significant effects (Saitoh et al. 2007).

Only two studies reported negative results in this domain (Rollnik et al. 2002; Irlbacher et al. 2006). Disappointingly, in one of these studies, more than one-third of the patients did not complete the full experimental design (Irlbacher et al. 2006). Concerning the other study, the stimulation was not focal, but performed with circular and double-cone coils, while the site and origin of pain were quite heterogeneous, including non-neuropathic pain syndromes (Rollnik et al. 2002). Nevertheless, in one patient of this latter study, pain relief was optimal 2 days after the rTMS session and lasted for 6 days. This observation was very similar to our own results. In a series of 14 patients with trigeminal neuralgia or thalamic pain, we found that pain level could be significantly reduced for 8 days by active vs. sham 10 Hz rTMS, the maximal analgesic effect being delayed by 2–4 days after the rTMS session (Lefaucheur et al. 2001b). This delay of action may be related to rTMS-induced plastic changes in cortical circuitry and needs to be taken into account in the design of rTMS studies in pain domain.

Thus, with regard to the analgesic efficacy of rTMS in chronic pain, several factors need to be considered: (1) the frequency of stimulation, (2) the intensity of stimulation, (3) the waveform of the magnetic pulses, (4) the site of stimulation, (5) the delay between the time of stimulation and the clinical effects, and (6) the duration of stimulation.

As aforementioned, rTMS should be performed at high frequency (10 Hz or more) to produce analgesic effects when applied to the motor cortex corresponding to the painful zone (contralateral to the side of pain). Another critical point is the intensity of stimulation: it seems better to set it below motor threshold. Stimulations performed above motor threshold were not associated with a better efficacy (Defrin et al. 2007). Our experience of chronic epidural MCS also showed that analgesic effects are produced at a low intensity of stimulation, sufficient to stimulate the superficial cortical layers (Nguyen et al. 2003, 2009). Therefore clinical results cannot be substantially improved by increasing stimulus intensity.

The waveform of the magnetic pulse is rarely questioned. All relevant rTMS studies on pain were performed using a figure-of-eight coil with a posteroanterior orientation and delivering biphasic pulses. However, biphasic pulses were found more efficient when the current was induced with an anteroposterior direction (Kammer et al. 2001). In addition, monophasic pulses were shown to provide stronger aftereffects on cortical activity than biphasic pulses using rTMS (Sommer et al. 2002; Arai et al. 2005). Thus, rTMS efficacy might improve by changing pulse waveform. This issue should be addressed in the future.

The efficacy of rTMS also seems to depend on a precise targeting, at least regarding M1 stimulation. For example, high-frequency rTMS failed to produce

significant analgesia when it was nonfocally applied with a circular coil (Rollnik et al. 2002). In a series of 60 patients with chronic neuropathic pain of various origins and locations, Lefaucheur et al. (2004b) found that facial pain was relieved more than hand pain when the hand motor area was stimulated. In another study, rTMS was found more effective when the stimulation site was adjacent to the cortical representation of the painful zone, rather than within the painful zone itself (Lefaucheur et al. 2006b). In fact, even if the target is the motor cortex, there are still many uncertainties about the precise location of the optimal stimulation site in this region. The use of a navigation system, integrating the individual data of brain magnetic resonance imaging, is very useful for this purpose (Ahdab et al. 2010; Lefaucheur 2010). The results of navigated rTMS studies are expected soon to clarify this point.

Another important issue is the latency of the analgesic effects. Following a single session of rTMS administered over M1, Lefaucheur et al. (2001b) found that the maximal analgesic effect was delayed for 2–4 days and that pain level could remain significantly reduced for about a week. This time course is similar to what is observed for chronic epidural MCS: clinical changes are delayed for several days after switching *ON* or *OFF* the stimulator or after modifying the parameters of stimulation (Nguyen et al. 2003, 2009). Expression of secondary messengers and time-consuming processes of synaptic plasticity in cortical circuitry could not explain why the effects are delayed, but rather why they last and are stabilized beyond the time of stimulation.

Nevertheless, analgesic effects resulting from a single rTMS session are too short lived to be compatible with a durable control of chronic pain. Repeated rTMS sessions on consecutive days are able to produce cumulative effects. Two studies clearly showed that long-lasting neuropathic pain relief could be obtained following a 5-day protocol of 20 Hz rTMS of M1 (Khedr et al. 2005; Ahmed et al. 2011). These studies included patients with post-stroke pain (Khedr et al. 2005), trigeminal neuropathic pain (Khedr et al. 2005), or phantom limb pain due to amputation (Ahmed et al. 2011). More recently, a third study was reported, based on a 10-day protocol of 5 Hz rTMS of M1 in a multicenter series of 64 patients with chronic neuropathic pain of various origins (Hosomi et al. 2013). Modest but significant pain reduction was found following active vs. sham rTMS, but a rather low frequency of stimulation (5 Hz) and a limited number of pulses (500) per session were used. Hosomi et al. (2013) concluded that repeated daily rTMS therapy could be clinically useful in responders, but they did not study the long-term efficacy of rTMS with the help of a maintenance protocol. A maintenance protocol of motor cortex rTMS for more than 5 months was first performed in patients with fibromyalgia (Mhalla et al. 2011). In this sham-controlled study, active rTMS reduced pain significantly to at least a month after the last stimulation session. In a more recent naturalistic study, high-frequency rTMS delivered to the motor cortex for more than 6 months was found to be able to relieve chronic refractory facial pain of various types, including cluster headache (Hodaj et al. 2015). These results suggest that rTMS protocols could induce long-lasting effects, compatible with therapeutic use in clinical practice (Lefaucheur 2011). However, the efficacy of motor cortex rTMS

still needs to be strengthened in terms of increasing the responder rate and the intensity of analgesic effects to a clinically meaningful level, including a significant improvement of the quality of life.

In chronic pain syndromes, rTMS could also be used as an add-on therapy, combined with medications or physical therapy. This strategy has been successfully developed in a recent study reported by Picarelli et al. (2010). These authors performed 10 daily sessions of 10 Hz rTMS over M1 in 23 patients with refractory pain due to complex regional pain syndrome (CRPS) type I concomitantly treated with the best medical treatment. Active rTMS produced significantly greater analgesic effects than sham rTMS over the 3 weeks of treatment, with positive effects on the different aspects of pain. This result also opens the perspective for the clinical use of rTMS in combination with other therapeutic approaches in pain patients.

Another application of rTMS in clinical practice is derived from the correlation between the analgesic responses to motor cortex rTMS and to surgically implanted MCS. First, we reported the case of a patient with chronic pain, who was a good responder to repeated rTMS sessions and experienced later a durable pain relief after surgical implantation of a cortical stimulator (Lefaucheur et al. 2004a). This case, as others (André-Obadia et al. 2006; Hosomi et al. 2008), suggested that rTMS could predict the outcome of a subsequent chronic epidural MCS. In a recent study of a large series of 59 implanted patients, we observed that a positive response to rTMS (pain score decrease by more than 30 % following verum vs. sham rTMS) was always associated with a good surgical outcome (pain score decrease by more than 50 %) in the long term (Lefaucheur et al. 2011). In contrast, the absence of response to motor cortex rTMS sessions did not indicate the result of the implanted procedure, except, maybe, in the long term (André-Obadia et al. 2014). The value of rTMS could be especially to confirm the indication of epidural MCS implantation. In this specific use, active rTMS sessions must be controlled by sham rTMS sessions to exclude placebo responders who are not good candidates for implantation. The order of these different interventions is perhaps not insignificant, since sham rTMS could induce significant analgesia only when preceded by a successful active stimulation (André-Obadia et al. 2011).

10.3 Mechanisms of Action

The strength-duration relationship of membrane properties makes fibers of passage more excitable than local cell bodies at the stimulation site for all types of brain stimulation techniques commonly used in therapeutics (Nowak and Bullier 1998a, b; McIntyre and Grill 2002). Therefore, the mechanisms of action of therapeutic neurostimulation must be modeled in terms of activated neural circuits with potentially remote effects, and not as local brain excitation or inhibition. Axonal excitation can give rise to both antidromic and orthodromic volleys. Antidromic volleys reach the neural structures from which efferents arise, while orthodromic volleys induce postsynaptic excitation or inhibition in cortical or deep brain targets. The axons recruited by cortical stimulation can be short fibers of intracortical

interneurons, as well as afferent or efferent fibers connected with distant structures (Lefaucheur 2008a). The analgesic effects of epidural MCS were shown to be induced by the preferential recruitment of horizontal cortical fibers, running parallel to the surface in the superficial layers of the crown of the precentral gyrus (Holsheimer et al. 2007a, b; Manola et al. 2007). The descending volleys elicited by epidural MCS are similar to those elicited by rTMS for producing analgesic effects (Lefaucheur et al. 2010a). The figure-of-eight coil used to perform motor cortex rTMS needs to be oriented parallel to the interhemispheric midline (André-Obadia et al. 2008), inducing current from anterior to posterior into the brain (according to the direction of the second phase of a biphasic TMS pulse). However, some uncertainty remains regarding the nature and connections of the neuronal circuits that are activated within the precentral gyrus (Lefaucheur 2006; Nguyen et al. 2011).

Early studies by Tsubokawa et al. (1991a, b) showed that MCS acted through a reduction in pain-related thalamic hyperactivity, which suggested that this technique involved an antidromic modulation of the thalamocortical pathways. Recent studies confirmed that the integrity of the thalamocortical tract was required to mediate the antinociceptive effects of 10 Hz rTMS (Goto et al. 2008; Ohn et al. 2012). The connections between afferent fibers from thalamic nuclei and pyramidal cells are thought to have an important role in the control of nociception (Villanueva and Fields 2004). This hypothesis was further supported by the demonstration of an improvement in sensory discrimination in pain patients treated by epidural MCS (Drouot et al. 2002). High-frequency rTMS delivered to the motor cortex also can modulate the perception of innocuous thermal stimuli or acute provoked pain applied in the painful region of patients with neuropathic pain (Lefaucheur et al. 2008b, 2010b). Sensory discrimination improvement appeared to be specific for thermo-nociceptive signals conveyed by the spinothalamic tract. This precludes a mechanism of pain relief due to the reinforcement of the lemniscal "gate control" over the nociceptive system. The functional integrity of the lemniscal system is essential to the efficacy of spinal cord stimulation (Sindou et al. 2003), but not of MCS (Garcia-Larrea et al. 1999).

Brain imaging studies showed that implanted MCS led to regional cerebral blood flow changes in the thalamus, the insula, and upper brain stem structures (Peyron et al. 1995, 2007; Garcia-Larrea et al. 1999; Garcia-Larrea and Peyron 2007). These structures are potentially involved in thermal sensation processing (Casey et al. 1996; Davis et al. 1998), and thereby they could mediate the associated effects of MCS on spontaneous pain and thermo-nociceptive stimuli perception. Thus, MCS might reduce pain-related hyperactivity in thalamic relays or interfere with abnormal thalamothalamic or thalamocortical oscillations, via corticothalamic projections and connections between thalamic nuclei.

It was also demonstrated that MCS could activate descending pathways, leading to reinforced or restored inhibitory control of nociceptive transmission in the dorsal horns of the spinal cord, as shown by neuronal recordings in animal models (Senapati et al. 2005; Rojas-Piloni et al. 2010) and by the increase in nociceptive spinal (RIII) reflexes in pain patients when MCS is switched *ON* (Peyron et al. 1995; Garcia-Larrea et al. 1999). These descending controls could take place in

various brain stem or spinal cord nuclei and be involved in the process of pain relief resulting from MCS. This hypothesis is reinforced by the low rate of efficacy observed in patients with brain stem stroke or spinal cord lesion in response to motor cortex rTMS (Lefaucheur et al. 2004b).

However, brain imaging studies (Peyron et al. 1995, 2007; Garcia-Larrea et al. 1999; Garcia-Larrea and Peyron 2007) also showed that MCS could activate other structures in the superficial or deep brain that are rather involved in the affective, cognitive, and emotional aspects of pain, such as the cingulate and orbitofrontal cortices. Tamura et al. (2004) also showed by single-photon emission computed tomography that the beneficial effects of motor cortex rTMS on capsaicin-induced acute pain correlated with an activation of the caudal part of the anterior cingulate cortex and an inhibition of the medial prefrontal cortex. These effects on limbic structures, such as those described on descending inhibitory controls, could result from opioidergic mechanisms. Recent imaging studies showed that MCS enhanced the release of endogenous opioids in various brain structures, and this was correlated to pain relief when the release was observed in the cingulate cortex and periaqueductal gray matter (PAG) (Maarrawi et al. 2007, 2013). The fact that the injection of naloxone, an opioid receptor antagonist, could significantly decrease the analgesic effects induced by high-frequency rTMS of the motor cortex confirmed the involvement of endogenous opioid systems in these effects (de Andrade et al. 2011). In a case of acute provoked pain, naloxone was also found to block the analgesic effect produced by rTMS delivered at 20 Hz over the contralateral parietal cortex (Amassian et al. 1997). Finally, an elevation of serum beta-endorphin concentration was found in patients with phantom limb pain treated by a series of five daily sessions of rTMS delivered at 20 Hz over the motor cortex that produced long-lasting pain relief (Ahmed et al. 2011).

In terms of neurotransmitters, the mechanisms of action of MCS could also involve inhibitory GABAergic transmission. Intracortical GABAergic circuits can be assessed by a paired-pulse TMS technique, which measures the percentage of intracortical inhibition (ICI) of motor evoked potentials (MEPs). Inhibition of MEPs is reduced in many patients with neurological disease, including those with neuropathic pain in the hemisphere contralateral to the painful zone. We demonstrated that high-frequency rTMS of the motor cortex could restore ICI in patients with neuropathic pain and that this restoration correlated with the degree of pain relief (Lefaucheur et al. 2006a). This result was confirmed by studies of other types of pain (Mhalla et al. 2011) or based on other types of TMS protocols (Lefaucheur et al. 2012), suggesting that the analgesic effects could involve a reinforcement of intracortical GABAergic inhibition. An increased ICI was also found to be associated with the analgesic effects of rTMS delivered at high frequency over the left dorsolateral prefrontal cortex (DLPFC) after capsaicin application on hand skin of healthy subjects (Fierro et al. 2010). The increase in ICI following high-frequency subthreshold rTMS in chronic pain patients is opposite to what is observed in naive healthy subjects (Maeda et al. 2000; Peinemann et al. 2000). Interestingly, motor cortex inhibition is associated with the existence of 20 Hz cortical oscillations that are abolished in the presence of chronic or provoked pain (Juottonen et al. 2002;

Raij et al. 2004). By restoring such oscillatory activity in the primary motor cortex, MCS could restore defective inhibitory mechanisms.

Thus, the mechanisms of action of MCS probably involve various types of neural transmission and neural circuits in response to the activation of fibers, which run parallel to the cortical surface in the precentral gyrus (Nguyen et al. 2011). This could result in the orthodromic activation of corticofugal pathways, as in the antidromic activation of thalamocortical pathways. The capacity of MCS to act on various neural structures and pathways involved in pain modulation probably explains the remarkable analgesic effect of this technique. Similar patterns of fiber activation can be produced by invasive epidural cathodal stimulation and by TMS using a figure-of-eight coil with an anteroposterior orientation parallel to the interhemispheric midline.

10.4 Other Cortical Targets

Cortical targets other than the motor cortex have been proposed in the treatment of neuropathic pain using implanted MCS, especially the somatosensory cortex (De Ridder et al. 2007). Some studies have reported the existence of pain relief from postrolandic cortical stimulation (Canavero 1995; Canavero and Bonicalzi 2002), and some experimental data support the analgesic effect of primary or secondary somatosensory cortex stimulation (Kuroda et al. 2000). However, in line with Tsubokawa's work, most research teams have found that stimulation using precentral contacts was more efficacious than stimulation using postcentral ones, when the MCS lead was positioned perpendicular to the central sulcus. The results of a study that used navigated rTMS confirmed that only the stimulation of M1, but not of adjacent areas (such as the postcentral gyrus (S1) and the premotor or supplementary motor area), could provide a significant relief of neuropathic pain (Hirayama et al. 2006). In contrast, 1 Hz rTMS applied over the right secondary somatosensory cortex (SII) was found to reduce chronic visceral pain due to chronic pancreatitis (Fregni et al. 2005). In this latter study, the rTMS target was also defined by means of a navigation system. The same team has recently reported the results of a phase II, sham-controlled clinical trial assessing the effects of daily sessions of 1 Hz rTMS over the right SII for 10 days in patients with chronic pancreatitis and severe visceral pain (Fregni et al. 2011). They found a significant reduction in pain after real rTMS that lasted for at least 3 weeks following treatment. Nevertheless, stimulation over the anterior bank of the central sulcus remains the preferred targeting strategy for analgesic cortical stimulation, at least for neuropathic pain.

Patients with neuropathic pain could also benefit from dorsolateral prefrontal cortex stimulation. Borckardt et al. (2009) performed three real and three sham sessions of 10 Hz rTMS over the left DLPFC in four patients with chronic neuropathic pain. Real rTMS produced a significant improvement in average daily pain in three of the four participants, independently of changes in mood. More recently, Sampson et al. (2011) applied 15 sessions of 1 Hz rTMS (1600 stimulations/session) to the right DLPFC in 9 subjects with refractory neuropathic pain over 3 weeks. Four

patients improved by more than 50 % in pain ratings up to the end of the 3-month follow-up. Both left DLPFC stimulation at high frequency and right DLPFC stimulation at low frequency could be valuable in patients with chronic pain, as it is the case in patients with depression. The best analgesic effects provided by rTMS of the DLPFC were reported following ten sessions of left-sided high-frequency stimulation in a series of patients with fibromyalgia (Short et al. 2011).

Conclusions

Significant analgesic effects of rTMS have been found in several studies of patients with chronic neuropathic pain of various origins, even when the placebo effect was appropriately controlled. Concerning rTMS, M1 stimulation at high frequency was shown to reduce pain scores by 20–45 % following active stimulation and by less than 10 % following sham stimulation. Regarding individual results, 35–60 % of the published patients have been considered as good responders to rTMS (more than 30 % pain relief following active rTMS).

Analgesic effects were obtained whatever the origin of pain, including the usual indications of surgically implanted MCS that are post-stroke pain (mainly thalamic stroke) and facial pain due to trigeminal neuropathy, as well as other causes of neuropathic pain, like spinal cord injury, root or brachial plexus avulsion, or peripheral nerve trunk lesion. Actually, it is not possible to determine an overall order of efficacy of noninvasive cortical stimulation with respect to pain diagnoses.

The strategies using rTMS to treat chronic neuropathic pain still remain to be optimized. What is accepted is that negative rTMS results can be attributed to a too low frequency of stimulation (5 Hz or less, at least for the stimulation of the motor cortex contralateral to a localized neuropathic pain) or too few pulses per session (500 or less). The optimal site of stimulation also remains an open question. Targeting procedures are expected to improve with the development of image-guided navigation using morphological or functional brain imaging. A practical algorithm concerning the implementation of rTMS in the treatment of neuropathic pain is shown in Fig. 10.1.

Despite their statistical significance, rTMS effects are rather modest and short lasting on a clinical level, and this is a major limit for a routine therapeutic use in patients with chronic pain. Invasive epidural stimulation can still be considered as the best approach for long-term management, unless the clinical relevance of maintenance treatment based on repeated sessions of rTMS is demonstrated. Increasing the total number of pulses per session and repeating the sessions for several days or weeks are surely able to enhance and prolong rTMS-induced analgesia. Table 10.1 presents the current evidence of the analgesic effects produced by sham-controlled protocols of repeated sessions of high-frequency rTMS of the motor cortex. Future investigation should also address the interindividual variability of the analgesic effects provided by cortical stimulation, the priming influence of various analgesic medications, and the characterization of the significant predictors of efficacy.

Nowadays, various noninvasive and invasive methods of neurostimulation are developing increasingly as therapeutic options for chronic neuropathic pain.

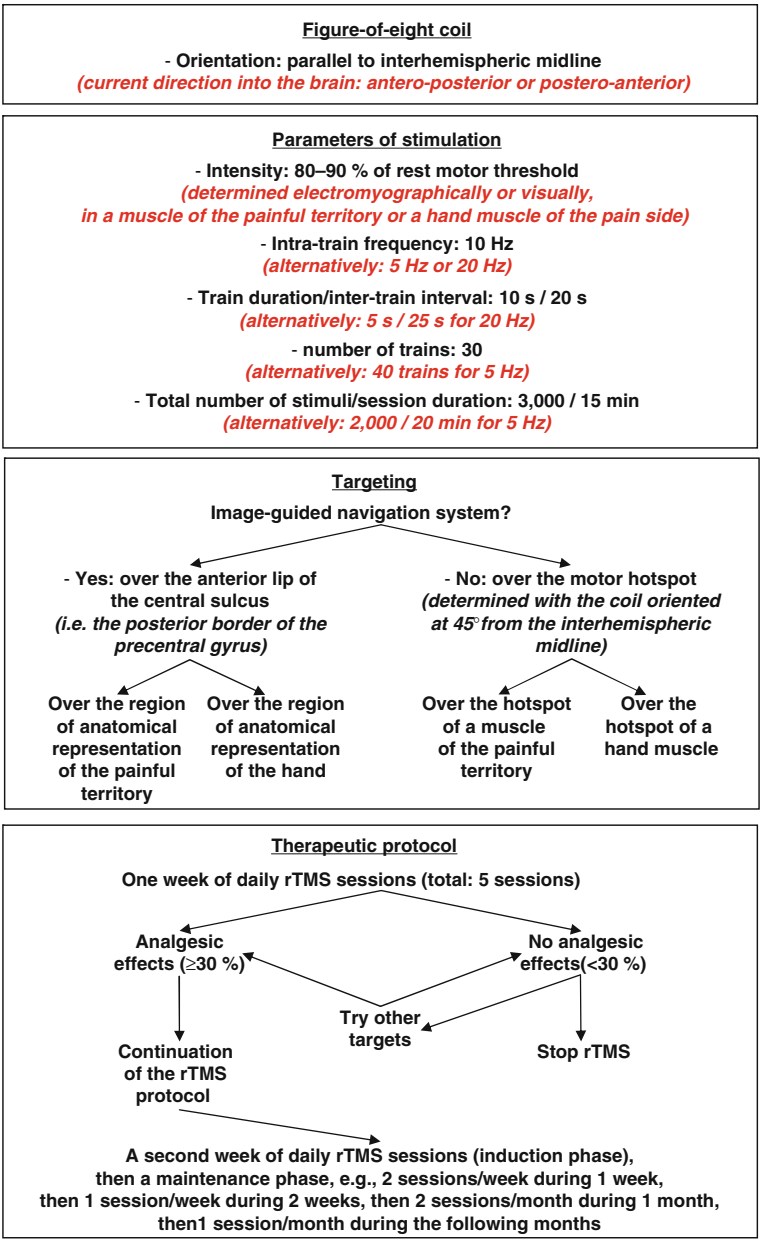

Fig. 10.1 Practical algorithm on the implementation of rTMS in the treatment of neuropathic pain

Therefore, the main challenge for pain specialists may be to define the best neurostimulation protocol to treat a given patient, according to the pathophysiological mechanisms of pain involved in this patient.

Table 10.1 Evidence of the analgesic effects produced by sham-controlled protocols of repeated sessions of high-frequency rTMS of the motor cortex using a figure-of-eight coil

Reference	Study type and population	Intervention (parameters of stimulation)	Outcome measures, main results, conclusion (grade)
Khedr et al. (2005)	Parallel arms: active vs. tilted coil 48 patients (active, 28; control, 20): trigeminal neuralgia (24), post-stroke pain (24)	20 Hz, 80 % RMT, hand M1 contralateral to pain side, 2000 pulses, 5 sessions	Significant analgesic effect of active rTMS on both VAS and LANSS up to 2 weeks post-rTMS Active rTMS: 45 % (end of rTMS) to 40 % (+2 weeks) of responders. Sham rTMS: 5 % (end of rTMS) to 2 % (+2 weeks) of responders High grade for rTMS efficacy (large sample size; no adverse effects)
Ahmed et al. (2011)	Parallel arms: active vs. tilted coil 27 patients (active, 17; control, 10): amputees with phantom limb pain	20 Hz, 80 % RMT, hand M1 contralateral to pain side, 2000 pulses, 5 sessions	Significant analgesic effect of active rTMS on both VAS and LANSS up to 2 months post-rTMS Increase in serum beta-endorphin after active, but not sham, rTMS, without any correlation with VAS, LANSS, or HDRS/HAM-A changes High grade for rTMS effects (duration of follow-up; no adverse effects)
Fricova et al. (2013)	Parallel arms: active vs. sham coil 36 patients (active vs. control, unknown numbers): 23 orofacial pain and 13 not defined patients	10 Hz, 85–95 % RMT, M1 contralateral to pain side, 600 pulses, 5 sessions	Significant analgesic effect of active rTMS on VAS compared to sham after the 1st to the 3rd session (−1.5 vs. −0.5 point) No change in tactile detection threshold after active and sham rTMS Low grade for rTMS effects (small sample size, few pulses per session, and poorly described population, methods, and results; no adverse effects)
Fricova et al. (2013)	Parallel arms: active vs. sham coil 23 patients (active, 13; control, 10): facial pain secondary to dental surgery (11), secondary to trigeminal nerve lesion (6), without clear organic substrate (6)	20 Hz, 95 % RMT, M1 contralateral to pain side, 720 pulses, 5 sessions	Significant analgesic effect of active rTMS on VAS compared to sham after the 3rd session to 2 weeks after the last session (−2 vs. −0 point) Similar reduction of warm detection threshold after active and sham rTMS. Reduction of tactile detection threshold after active rTMS Low grade for rTMS effects (small sample size, few pulses per session, and poorly described population, methods, and results; no adverse effects)

(continued)

Table 10.1 (continued)

Reference	Study type and population	Intervention (parameters of stimulation)	Outcome measures, main results, conclusion (grade)
Hosomi et al. (2013)	Crossover (random order), active vs. realistic sham; washout period, 17 days at least 64 patients: post-stroke pain (52), spinal cord lesion (7), phantom limb pain (3), root or nerve lesion (2)	5 Hz, 90 % RMT, M1 corresponding to the painful region, 500 pulses, 10 sessions	Significant analgesic effect of active rTMS on VAS compared to sham, but only 4 % of difference in VAS reduction rate between the two groups Significant improvement of SF-MPQ and PGIC after active rTMS. PGIC change not lasting. No change in BDI Medium grade for rTMS effects (large sample size, duration of treatment, but few pulses per session; minor and transient adverse effects (12 % active group vs. 6 % sham group): headache, dizziness)
Khedr et al. (2015)	Parallel arms: active vs. tilted coil 34 patients (active, 17; control, 17): relative to cancer or its treatment	20 Hz, 80 % RMT, hand M1 contralateral to pain side, 2000 pulses, 10 sessions	Significant analgesic effect of active rTMS on VRS, VAS, and LANSS scores at the end and up to 2 weeks after rTMS protocol. No more effect at 4 weeks after rTMS protocol Antidepressant effect lasting up to 6 weeks after active rTMS (HDRS) Medium grade for rTMS effects (poor clinical definition of the patients; no adverse effects)

RMT rest motor threshold, *M1* primary motor cortex, *VAS* visual analog scale, *LANSS* Leeds assessment of neuropathic symptoms and signs pain scale, *HDRS* Hamilton depression rating scale, *HAM-A* Hamilton anxiety rating scale, *SF-MPQ* short-form McGill pain questionnaire, *PGIC* patient global impression of change, *BDI* Beck depression inventory, *VRS* verbal rating scale

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Therapeutic Applications of rTMS for Tinnitus

11

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Abstract

Tinnitus, the phantom perception of sound in the absence of a corresponding acoustic signal, is a frequent disorder which is difficult to treat. Cognitive behavioral therapy can effectively facilitate the habitation to the phantom sound, but there exist no established therapeutic options for reducing the intensity or the loudness of tinnitus. Thus, there is an urgent need for more effective treatment approaches.

Functional imaging studies in tinnitus patients have revealed alterations in both auditory and nonauditory brain areas, which represent potential targets for treatment via repetitive transcranial magnetic stimulation (rTMS). Single sessions of rTMS over the temporal or temporoparietal cortex have been successful in transiently reducing tinnitus perception. Many but not all randomized controlled trials have revealed that repeated sessions of rTMS result in a significant reduction of tinnitus severity. However, available studies vary in methodological quality, variability in treatment results is high both within and across studies, effect sizes of rTMS in the reduction of tinnitus severity are only moderate, and only few studies assessed long-term outcome. Thus, even if quality of evidence is high, currently only a weak recommendation can be given for the use of rTMS for the treatment of chronic tinnitus.

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11.1 Introduction

Tinnitus is characterized by the perceived sensation of sound in the absence of a corresponding external stimulus. Tinnitus can take the form of continuous buzzing, hissing, or ringing, or a combination of these or other characteristics. It can be heard in one or both ears, but it can also be referred to the head. Tinnitus can occur intermittently or have a pulsatile character. The intensity of the phantom sound can vary from a subtle noise just above hearing threshold to high-intensity sounds which cannot be masked by any external noise.

Tinnitus is classified according to whether the perceived noise has its source within the patient's body known as *objective tinnitus* or *somatosounds* (e.g., myoclonic contractions of the tensor tympani muscle) or if it is only perceivable to the patient and lacks a specific sound source, namely, *subjective tinnitus*. Subjective tinnitus is by far the most common form, and it is the scope of the present chapter.

Based on recent data, tinnitus occurs in 25.3 % of American adults with 7.9 % experiencing it frequently (Shargorodsky et al. 2010). Epidemiological studies reveal comparable prevalence rates for Europe (Axelsson and Ringdahl 1989; Krog et al. 2010).

Hearing loss is the most important risk factor for the development of tinnitus. Tinnitus occurs typically at the frequency and the side of the hearing loss (e.g., somebody with a left-sided hearing loss around 4 kHz develops typically a tinnitus with a frequency of 4 kHz at the left side). Accordingly, it has been proposed that tinnitus results from the effort of the brain to compensate for reduced neuronal input, similar to the generation of phantom pain after limb amputation (Tonndorf 1987; Moller 2000). Alterations in the central auditory system detected in animals after noise trauma, such as increased intensity and synchrony of neuronal firing and altered tonotopic organization, have been hypothesized to represent the neuronal correlates of tinnitus (Eggermont and Roberts 2004). Recent research has increasingly identified the involvement of nonauditory brain areas, such as frontal and limbic cortical areas (Adjamian et al. 2009; Lanting et al. 2009; De Ridder et al. 2014). Moreover, it has been generally recognized that tinnitus is clinically heterogeneous, with respect to its etiology, its perceptual characteristics, and its accompanying symptoms. In addition to acoustic (the unwanted sound, i.e., most commonly known as the perception of "ringing in the ears") and attentional (the extent to which the person is aware of the sound) components, tinnitus can also involve emotional, cognitive, and memory components. Fortunately, not all people who perceive tinnitus are suffering from it. However, there are many patients with tinnitus who report symptoms such as frustration, annoyance, anxiety, depression, irritation, and concentration difficulties. These symptoms are highly relevant for the perceived tinnitus severity (Langguth 2011). Thus, tinnitus represents a highly prevalent and potentially distressing condition that places a huge burden on many patients and significantly impairs their quality of life.

Available treatments for the management of tinnitus are diverse, but all of limited efficacy. The most established treatments include counseling and cognitive behavioral therapies, different forms of sound therapies, and methods that attempt to

compensate for hearing loss (such as hearing aids and cochlear implants) for use in patients whose tinnitus is caused by deprivation of signals to the auditory nervous system. Several forms of magnetic or electrical brain stimulation have been investigated for the treatment of tinnitus in the last decade (Langguth and De Ridder 2013). All these treatment approaches are still at early stages of development, and their further development will critically depend on advances in the understanding of the pathophysiology of the different forms of tinnitus.

11.2 Pathophysiology

Although tinnitus is frequently triggered by peripheral mechanisms (e.g., cochlear impairment), it usually persists after auditory nerve section (Jackson 1985), highlighting the critical involvement of central mechanisms in its pathophysiology. Abnormal activity in the central auditory pathways has been described in animals after noise trauma (Eggermont 2005) and also in patients with tinnitus (Adjamian et al. 2009; Lanting et al. 2009). These alterations can be explained by mechanisms of homeostatic plasticity at several levels along the auditory pathway in order to compensate for the reduced auditory input (Norena 2011; Schaette and Kempter 2006; Yang et al. 2011; De Ridder et al. 2014). Based on magnetoencephalographic (MEG) and electroencephalographic (EEG) studies investigating spontaneous brain activity associated with tinnitus, it has been proposed that tinnitus is related to gamma band activity in the auditory cortex, analogous to gamma band activity in normal auditory processing (van der Loo et al. 2009; Ortmann et al. 2011). The emergence of gamma activity may be enabled by a lack of inhibitory function in the auditory cortex which in turn is reflected by decreased alpha activity (Weisz et al. 2005, 2007a).

Importantly, activity changes in the central nervous system are not restricted to auditory pathways (Lanting et al. 2009). Rather, they can be conceived as alterations of a network involving both auditory and nonauditory structures (De Ridder et al. 2011; Schlee et al. 2008, 2009). The involvement of nonauditory brain areas may be explained by the notion that conscious auditory perception requires auditory cortex activation embedded in the coactivation of consciousness supporting networks (Demertzi et al. 2012), such as the salience network comprising anterior insula, anterior cingulate, and thalamus (Sadaghiani et al. 2009). Moreover, pathophysiological models of tinnitus have to account for the affective component of tinnitus, which can be more or less pronounced (Hebert et al. 2012; Langguth et al. 2011). By contrasting tinnitus patients with more and less distress, differences in neuronal activity could be identified in a network consisting of the anterior cingulate cortex, the anterior insula, and the amygdala (De Ridder et al. 2006; Schlee et al. 2008; Vanneste et al. 2010). This nonspecific "distress network" is similarly activated in chronic pain or somatoform disorders (De Ridder et al. 2011). Comparable to chronic pain syndromes, memory mechanisms may play a role in the persistence of the phantom percept, as well as in the reinforcement of the associated distress (De Ridder et al. 2011). In accordance with this notion, hippocampal involvement has been documented in animal models of tinnitus (Goble et al. 2009; Kraus et al. 2010)

and by neuroimaging in tinnitus patients (Landgrebe et al. 2009). Presumably there is an important mutual interaction between the different involved networks which may be relevant for the maintenance of tinnitus, even after disappearance of the initial trigger. In this context, it has been suggested that salience-related brain circuits in the subgenual cingulate cortex/nucleus accumbens area are relevant for maintaining tinnitus by exerting a direct impact on auditory pathways via the reticular thalamic nucleus (Rauschecker et al. 2010; Cheung and Larson 2010). Importantly, using resting-state MEG (Schlee et al. 2009) and EEG (Vanneste et al. 2011b) studies, it has been shown that the tinnitus-related spontaneous activity and functional connectivity changes over time.

In summary, there is compelling evidence for a dynamically changing widespread tinnitus brain network, which includes sensory auditory areas as well as cortical regions involved in perceptual, emotional, memory, attentional, and salience functions (De Ridder et al. 2011) (see Fig. 11.1).

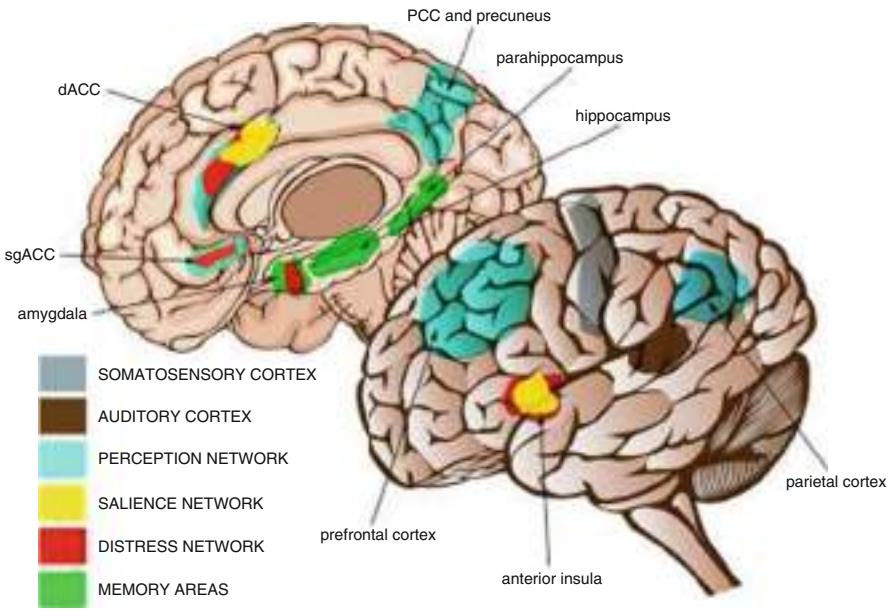

Fig. 11.1 Tinnitus networks. Brain networks involved in phantom perception. Increased activity in the auditory cortex (*brown*) as a consequence of auditory deprivation is necessary, but not sufficient for tinnitus perception. The stimulus becomes consciously aware if auditory activity is connected to a larger coactivated awareness network involving subgenual (*sgACC*) and dorsal anterior cingulate cortex (*dACC*), posterior cingulate cortex (*PCC*), precuneus, parietal cortex, and frontal cortex (*blue*). Salience to the phantom percept is reflected by activation of dACC and anterior insula (*yellow*). Tinnitus annoyance is reflected by coactivation of a nonspecific distress network consisting of the anterior cingulate cortex (*sgACC* and *dACC*), anterior insula, and amygdala (*red*). Memory mechanisms involving the parahippocampal area, amygdala, and hippocampus (*green*) play a role in the persistence of the phantom percept (Modified from (De Ridder et al. 2011); Copyright 2011 National Academy of Sciences, U.S.A.)

11.3 Tinnitus Measurement

As tinnitus is a purely subjective phenomenon, measurement of treatment outcome is not trivial. Tinnitus loudness can be either assessed by psychoacoustic measurements (loudness matching or minimal masking level) or by visual analogue or numeric rating scales. The impact of tinnitus on quality of life is usually assessed by validated questionnaires (Zeman et al. 2014). As psychoacoustic measures of tinnitus loudness have shown only limited test-retest reliability (Henry and Meikle 2000), tinnitus loudness assessment by visual analogue scales or numeric rating scales may provide more useful information (Adamchic et al. 2012). Validated questionnaires are the recommended primary outcome measurement for clinical trials (Langguth et al. 2007). However, there exist several validated questionnaires which assess similar but not identical constructs (Milerova et al. 2013). Even if the scores of different questionnaires correlate with each other (Zeman et al. 2012), comparability across studies using different questionnaires is impaired.

11.4 Rationale for the Application of rTMS in Tinnitus

As mentioned in the introduction, tinnitus is related to altered activity of cortical networks involving also central auditory areas. Since rTMS has the ability to focally modulate cortical activity, it has been assumed that it can interfere with the tinnitus-related abnormal neural network activity and thereby influence the perception of tinnitus.

In a recent study, stimulation sites thought to be most effective in various neurological diseases were found to represent different nodes within the same brain network as defined by resting-state functional connectivity MRI (Fox et al. 2014). Based on this observation, one would expect that tinnitus can be modulated by targeting nodes of tinnitus-related abnormal cortical networks. Indeed, single sessions of rTMS over the temporal or temporoparietal cortex but also over the frontal and parietal cortex have been shown to reduce tinnitus transiently in a subgroup of tinnitus patients (for an overview, see (Langguth and De Ridder 2013)). With the goal to produce longer-lasting modulation of tinnitus-related cortical activity, repeated applications of rTMS have been investigated as a potential treatment for some forms of tinnitus. Thus, in summary, analogous to what has been proposed for implanted electrodes overlying the auditory cortex in tinnitus, only those patients who exhibit good functional connectivity between the stimulation target and the putative tinnitus network are likely to respond to neuromodulatory approaches (De Ridder and Vanneste 2014).

11.5 Clinical Effects of rTMS in Tinnitus

Based on the notion that tinnitus is related to auditory cortex hyperactivity, low-frequency rTMS has been applied with the aim to reduce tinnitus by reducing auditory cortex hyperactivity. Since this approach was first proposed (Eichhammer et al.

2003; Langguth et al. 2003), it has been investigated in an increasing number of studies applying low-frequency rTMS in long trains of 1200–2000 pulses repeatedly over 5–10 days (Table 11.1). Beneficial effects of low-frequency rTMS have been confirmed by many (Anders et al. 2010; Khedr et al. 2008, 2009; Plewnia et al. 2007b; Marcondes et al. 2010; Smith et al. 2007; Rossi et al. 2007) but not all further controlled studies (Piccirillo et al. 2013; Langguth et al. 2014; Hoekstra et al. 2013). Moreover, the degree of improvement and the duration of treatment effects varied across studies, probably due to differences in study design, stimulation parameters, and selection criteria of the participants.

11.6 Duration of Treatment Effects

While some studies demonstrated effects that outlasted the stimulation period for several months (Khedr et al. 2008, 2009; Marcondes et al. 2010) up to 4 years (Burger et al. 2011), others were not able to achieve long-lasting effects (Plewnia et al. 2007b; Rossi et al. 2007). One case report (Mennemeier et al. 2008) and a case series (Langguth et al. 2008b) suggest that patients who respond once to rTMS treatment also experience further positive effects from a second series of rTMS, but controlled studies investigating maintenance therapy are lacking.

11.7 Stimulation Frequency

Currently, it is also still unclear, whether low-frequency rTMS is the optimal stimulation frequency. Two studies demonstrated that 10 Hz and 25 Hz rTMS are at least as efficient as 1 Hz for tinnitus treatment (Khedr et al. 2008, 2009, 2010). High-frequency priming stimulation, which enhanced effects of low-frequency rTMS in a preclinical study (Iyer et al. 2003), has failed to enhance the therapeutic efficacy of low-frequency rTMS for the treatment of tinnitus (Langguth et al. 2008a). Also theta-burst stimulation has been investigated with conflicting results. In one study, ten sessions of continuous theta-burst TMS over the auditory cortex have reduced tinnitus loudness and tinnitus impairment (Chung et al. 2012). In contrast, bilateral continuous theta-burst over 4 weeks had no superior effect on tinnitus as compared to sham stimulation (Plewnia et al. 2012)

11.8 Stimulation Target

The optimal target for stimulation and the best method for coil positioning are still a matter of debate (Langguth et al. 2010). Various neuroimaging methods reveal slightly different areas of abnormal neuronal activity in tinnitus, and accordingly different targets have been chosen for stimulation. Based on FDG-PET data that reveal increased neuronal activation predominantly of the left auditory cortex independent of tinnitus laterality (Arnold et al. 1996), this area has been chosen as treatment

Table 11.1 Effects of repeated sessions of rTMS in tinnitus patients

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Kleinjung et al. (2005)	14	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil	1 Hz, 110 % RMT	2000 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months)	III
Rossi et al. (2007)	16	Left TPC, F8c (navigation and 10–20 EEG system)	Tilted coil combined with electrical skin stimulation	1 Hz, 120 % RMT	1200 pulses, 5 sessions	Significant tinnitus reduction (no prolonged effect)	III
Khedr et al. (2008; 2009)	66 (active: 16, 17, 17; control: 16)	Left TPC, F8c (10–20 EEG system)	Stimulation of nonauditory cortical areas	1/10/25 Hz, 100 % RMT	1500 pulses, 10 sessions	Significant tinnitus reduction for all active conditions (prolonged effect up to 12 months); less efficacious for tinnitus with longer duration	III
Anders et al. (2010)	42 (active: 22; control: 20)	Auditory cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 110 % RMT	1500 pulses, 10 sessions	Significant tinnitus reduction (not initially, but at 3–6 months after the stimulation)	II

(continued)

Table 11.1 (continued)

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Marcondes et al. (2010)	19 (active: 10; control: 9)	Left superior temporal cortex, F8c (10–20 EEG system)	Sham coil	1 Hz, 110 % RMT	1020 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months); effect correlated to a reduced activity of inferior temporal cortices in SPECT	III
Mennemeier et al. (2011)	21	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil combined with electrical skin stimulation	1 Hz, 110 % RMT	1800 pulses, 5 sessions	Significant tinnitus reduction (43 % responders, 33 % improvement); no correlation with activity changes in PET	II
Piccirillo et al. (2011)	14	Left TPC, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz, 110 % RMT	1500 pulses, 10 sessions	Nonsignificant tinnitus reduction	III
Chung et al. (2012)	22 (active: 12; control: 10)	Left auditory cortex, F8c (navigation)	Sham coil	cTBS, 80 % RMT	900 pulses, 10 sessions	Significant tinnitus reduction; more efficacious on emotional component of tinnitus	III

Plewnia et al. (2012)	48 (active: 16, 16; control: 16)	Bilateral temporal cortex or TPC, F8c	Active stimulation behind the mastoid	cTBS, 80 % RMT	900 pulses, 20 sessions	Nonsignificant tinnitus reduction	III
Hoekstra et al. (2013)	50 (active: 25; control: 25)	Bilateral primary auditory cortex, F8c (navigation)	Sham coil	1 Hz, 110 % RMT	4000 pulses (2000 left, 2000 right), 5 sessions	Nonsignificant tinnitus reduction	I
Lee et al. (2013)	15	Left temporal cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 100 % RMT	1200 pulses, 10 sessions	Significant tinnitus reduction, negatively correlated to the duration of tinnitus	III
Piccirillo et al. (2013)	14	Left temporoparietal junction, F8c	Sham coil	1 Hz, 110 % RMT	20 sessions	Nonsignificant tinnitus reduction	III
Bilici et al. (2015)	75 (active 30, 15; control 30)	Left TPC, Cc	Sham coil	1/10 Hz, 110 % RMT	900 pulses (1 Hz) or 600 pulses (10 Hz), 10 sessions	Significant tinnitus reduction for all active conditions, less pronounced in combination with paroxetine	III

(continued)

Table 11.1 (continued)

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Langguth et al. (2014)	185 (active: 47, 48, 46; control: 44)	PET-guided temporal cortex, left temporal cortex, combined left temporal + prefrontal cortices, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz (temporal cortex), 20 Hz (prefrontal cortex), 110 % RMT	2000 or 4000 pulses, 10 sessions	Significant tinnitus reduction for all three active conditions, but no statistical significant difference in comparison to sham; better effects on a descriptive level for combined frontal and temporal rTMS	I

Studies were included in the table, when they (1) investigated the effects of repeated sessions of rTMS in tinnitus patients, (2) were randomized placebo-controlled trials, and (3) included at least ten patients receiving active stimulation, and (4) at least two comparable studies (same cortical target and same stimulation frequency) were published by independent groups before the end of the bibliographic search (September 2014). *Number of patients* refers to the number of patients who actually received rTMS therapy, excluding dropouts. In trials with parallel arms, the respective number of patients in the active and control groups is indicated. The absence of indication means a crossover design with both active and control conditions applied to all patients. In the *Results* column, the main results are usually summarized as a function of the significance of the effect of active rTMS *versus* control condition. *Class of the study* reflects the methodological quality of the study according to criteria proposed by the European Federation of Neurological Societies (Brainin et al. 2004). A class I study is an adequately data-supported, prospective, randomized, placebo-controlled clinical trial with masked outcome assessment in a representative population ($n \geq 25$ patients receiving active treatment). It should include (a) randomization concealment, (b) clearly defined primary outcomes, (c) clearly defined exclusion/inclusion criteria, (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences. A class II study is a randomized, placebo-controlled trial performed with a smaller sample size ($n < 25$) or that lacks at least one of the above-listed criteria a–e. Class III studies include all other controlled trials (According to Lefaucheur et al. (2014))

target in many studies. Whereas a first study revealed a relationship between PET activation in the auditory cortex and treatment outcome (Langguth et al. 2006), this finding could not be confirmed in a larger sample (Schecklmann et al. 2013). A recent study performing FDG-PET before and after treatment found no relationship between activation changes in the stimulated area and clinical outcome, questioning the use of FDG-PET for identification of the optimal treatment target.

Other imaging studies identified abnormalities predominantly in temporoparietal areas (Plewnia et al. 2007a). Based on fMRI (Smits et al. 2007) and MEG studies (Llinas et al. 1999; Muhlnickel et al. 1998; Weisz et al. 2007b), the primary involvement of the auditory cortex contralateral to the perceived tinnitus has been hypothesized (De Ridder 2010). A recent study confirmed this notion by demonstrating that rTMS over temporoparietal areas is more efficient when applied contralaterally to the perceived tinnitus than ipsilaterally (Khedr et al. 2010). However, this is somewhat contradictory to another recent finding that shows lower efficacy of left temporal rTMS in right-sided tinnitus as compared to left-sided tinnitus (Frank et al. 2010).

Pathophysiological concepts and neuroimaging findings are stressing the relevance of nonauditory areas in tinnitus (De Ridder et al. 2014). Therefore, stimulation protocols have been extended to the frontal cortex. In one pilot study, 32 patients received either low-frequency temporal rTMS or a combination of high-frequency prefrontal and low-frequency temporal rTMS (Kleinjung et al. 2008). Directly after therapy, there was an improvement of the tinnitus questionnaire score for both groups, but there were no differences between groups. Evaluation after 3 months revealed a remarkable advantage for combined prefrontal and temporal rTMS treatment. A pilot study demonstrated similarly a tendency toward increased efficacy when 1 Hz left temporal rTMS was preceded by 1 Hz right prefrontal rTMS (Kreuzer et al. 2011). These data indicate that modulation of both frontal and temporal cortex activity might represent a promising enhancement strategy for improving TMS effects in tinnitus patients.

It is known from animal experiments that neuronal plasticity can be enhanced by dopaminergic receptor activation (Bao et al. 2001). However, in pilot studies, the administration of neither 100 mg of levodopa nor 150 mg bupropion before rTMS was successful in enhancing rTMS effects in tinnitus patients (Kleinjung et al. 2009, 2011).

There is some evidence from several studies that the clinical characteristics of patients may affect the therapeutic outcome of rTMS in tinnitus patients. Several studies reported that patients who had their tinnitus for a shorter duration may have better treatment outcomes (Khedr et al. 2008; Kleinjung et al. 2007). However, when larger samples were analyzed, this effect could neither be confirmed nor other robust predictors for treatment outcome could be identified (Frank et al. 2010; Lehner et al. 2012).

11.9 Neurobiological Mechanisms of rTMS Effects in Tinnitus

The mechanisms by which rTMS exerts its clinical effects on tinnitus are still incompletely understood. The concept that 1 Hz rTMS reduces tinnitus by inducing long-term depression (LTD)-like effects on increased neuronal activity in the

auditory cortex has been challenged by the findings that (1) treatment outcome of 1 Hz rTMS is worse in patients with more pronounced auditory hyperactivity (Langguth et al. 2006) and that (2) both low- and high-frequency rTMS over the temporoparietal cortex exert beneficial effects on tinnitus (Khedr et al. 2008, 2010).

In line with these findings, a recent investigation in healthy controls has demonstrated that both low- and high-frequency rTMS over the temporal cortex reduce auditory cortex excitability as measured with the auditory-evoked P50 amplitude (Nathou et al. 2014)

FDG-PET scans before and after rTMS were not successful for identifying the neuronal correlates of rTMS-induced tinnitus reduction (Mennemeier et al. 2011). In particular, no relationship between the treatment-related change of metabolic activation of the auditory cortex and clinical effects could be detected (Mennemeier et al. 2011).

A study which investigated the effects of auditory cortex stimulation in healthy controls with voxel-based morphometry found alterations in the temporal cortex and in the thalamus, suggesting that temporal rTMS may influence thalamocortical processing (May et al. 2007).

The exact cortical region in which temporal rTMS exerts clinical effects in tinnitus patients is still a matter of debate (Langguth et al. 2010). It has been argued that the primary auditory cortex is difficult to reach by TMS, since it is located far from the brain surface in the Sylvian fissure in the lateromedial direction. Furthermore, following the tonotopic organization of the primary auditory cortex, the representation of low frequencies is located more lateral, whereas the representation of high frequencies is more medial. Thus, one would expect better outcomes in patients with low-frequency tinnitus since the related abnormalities in the auditory cortex are expected to be more lateral and should therefore be better reached by rTMS. However, such a relationship could not be demonstrated (Frank et al. 2010). It has been proposed that rTMS might exert direct effects on the superficial secondary auditory cortex which then further propagate to the primary auditory cortex, analogous to what has been described for electrical stimulation of the secondary auditory cortex in tinnitus. A recent study which used MEG to record auditory-evoked potentials suggests that rTMS induces changes in both primary and secondary auditory cortex activity (Lorenz et al. 2010). The auditory steady-state response, which is supposed to be generated in the primary auditory cortex, was more consistently influenced by rTMS, and its changes also correlated with perceptual changes (Lorenz et al. 2010). Also a very recent study which investigated the effects of paired associative auditory and cortical stimulation (Schecklmann et al. 2011) does not provide clear evidence where exactly temporal TMS interferes with auditory processing.

11.10 Methodological Considerations

Both tinnitus perception and distress are known to be susceptible to placebo effects (Dobie 1999). Therefore, evaluation of treatment efficacy requires adequate methodology for the control of nonspecific effects. Different kinds of sham treatments

have been suggested as control conditions. In addition to the sham coil system, which mimics the sound of the active coil without generating a magnetic field, an angulation of an active coil tilted 45° or 90° to the skull surface or a stimulation of nonauditory brain areas has been described (see Table 11.1). Finding an optimal control condition for treatment studies is also difficult because of limitations in blinding of patients and operators to different stimulus conditions and due to the fact that TMS itself results in auditory and somatosensory stimulation in addition to the cortical effect. Indeed, a very recent study provides empirical support for the relevance of a double mechanism consisting of a direct cortical modulating effect and an indirect effect via somatosensory-auditory interactions mediated through trigeminal and C2 nerve activation (Vanneste et al. 2011a). As a possible approach for differentiating the two effects, the use of a control condition involving electrical stimulation of the facial nerve has been proposed (Mennemeier et al. 2009; Rossi et al. 2007). Similarly, also interactions between the acoustic artifact of the coil and auditory cortical stimulation may be relevant (Schecklmann et al. 2011).

11.11 Safety Aspects

Even if rTMS is a safe technique (Wassermann 1998; Rossi et al. 2009), some precautions need to be met, mainly due to the theoretical risk of triggering a seizure (though extremely improbable with LF rTMS) or especially of inducing auditory changes because of the noisiness of rTMS at high intensities. The potential harm to hearing function has to be particularly considered in the treatment of tinnitus, since many tinnitus patients suffer from hearing loss. Actually, rTMS has recently been reported to transiently decrease the amplitude of the otoacoustic emissions, reflecting active cochlear effects (Tringali et al. 2012). Despite the absence of recognized auditory toxicity (Schonfeldt-Lecuona et al. 2012), some patients with tinnitus may complain of a worsening of hyperacusis and painful hypersensitivity to noises after rTMS therapy (Rossi et al. 2009). One recent study in tinnitus patients did not show any deterioration in hearing function after a treatment series of 20 sessions of theta-burst stimulation (Schraven et al. 2013). A clinically relevant side effect is the risk of worsening of tinnitus, which has been reported in several studies for a small subgroup of patients. However, little is known whether the worsening of tinnitus, reported in these patients after treatment, is only transient or longer lasting.

Conclusion

In summary, there are an increasing number of studies investigating rTMS for the treatment of tinnitus. Though encouraging, results must still be considered as preliminary due to small sample sizes, methodological heterogeneity, high inter-individual variability, and limited knowledge about the duration of therapeutic effects. Replication in multicenter trials with many patients and long-term follow-up are required before firm conclusions can be drawn (Landgrebe et al. 2008). Further clinical research is also needed to get a clear definition of subgroups of tinnitus patients which benefit most from rTMS and how their medical

histories, their comorbidities, and their medication may affect the outcome. Better understanding of the pathophysiology of the different forms of tinnitus and the neurobiological effects of rTMS will be critical for optimizing or even individualizing treatment protocols.

A few years ago, a Cochrane meta-analysis of rTMS for the treatment of tinnitus (Meng et al. 2011), which only included randomized controlled studies with parallel groups (Anders et al. 2010; Marcondes et al. 2010; Khedr et al. 2008), came to the conclusion that there is currently limited evidence for efficacy and that further studies are needed before firm conclusions can be drawn. Recently published evidence-based guidelines concluded that "LF (1 Hz) rTMS unilaterally applied to temporal or temporoparietal cortical areas can interact with an abnormal hyperactivity of auditory cortices that may constitute the neural correlate of tinnitus perception. Literature data showed that this type of rTMS protocol has a possible therapeutic efficacy in this clinical condition. The efficacy of active rTMS is superior to placebo in the treatment of subjective tinnitus, but the effects are usually partial and transient at clinical level" (Lefaucheur et al. 2014).

If the quality of evidence is rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines (Owens et al. 2010), one has to consider that the available randomized clinical trials have methodological limitations. They have all relatively small sample sizes, and the methodological quality of study conduct and study design is heterogeneous, resulting in a relatively high risk of bias, which may also contribute to the heterogeneity in the results of the available studies. Despite the obvious heterogeneity of the different studies, the results are not completely inconsistent. Most studies report beneficial effects of TMS with a small effect size. This effect reaches statistical significance in some studies, but not in others, resulting in a certain imprecision. Therefore, the certainty that the estimate of the treatment effect reflects the real effect is currently still limited.

With respect to directness, the most relevant limitation of the available studies is the short follow-up periods after intervention. For a chronic condition like tinnitus, the long-term outcome is most relevant. However, mostly all available studies used the reduction of tinnitus severity or tinnitus handicap, assessed at the end of treatment period with validated questionnaires, as primary outcome. Systematic assessment of long-term outcome has only been reported in few studies (Khedr et al. 2008, 2009).

Thus, in summary, the strength of evidence for a beneficial effect of rTMS on tinnitus has currently been judged as low. This means that further research is likely to change our confidence in the estimate of effect and is also likely to change the estimate (Owens et al. 2010). Thus, currently rTMS cannot yet be recommended for routine treatment of tinnitus. However, in consideration of the relatively limited therapeutic alternatives, the use of low-frequency rTMS over the temporal or temporoparietal cortex or the combination of high-frequency rTMS over the left DLPFC followed by low-frequency rTMS over the left temporal cortex can be justified in specific cases but should be embedded in a comprehensive management of the tinnitus patient (Langguth et al. 2013).

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Therapeutic rTMS in Neurology: Applications, Concepts, and Issues

12

Thomas Platz

Abstract

rTMS therapy has been shown to generate clinical benefits in a variety of conditions after stroke such as arm and leg paresis, spasticity, dysphagia, aphasia, and neglect, for motor deficits in Parkinson's disease, for impaired gait and spasticity in incomplete spinal cord injury (SCI) subjects, and for other frequently encountered clinical conditions such as tinnitus and neuropathic pain. The variability of the brain's response and any clinical effects to rTMS therapy still make it difficult to predict any individual's response. Nevertheless, the clinical benefits that can be achieved are at times remarkable and favor the clinical application of rTMS therapy. Issues such as the neurophysiological model of action, the selection of the target site, the type, the schedule, and the combinations of rTMS applications, as well as the question of combined rTMS and training therapy, are reflected for the different conditions treated.

12.1 Applications of rTMS in Clinical Neurology

The previous chapters in this book give an overview over conditions where rTMS interventions have been shown to produce clinical benefits. Indeed, in a variety of conditions after stroke such as deficits of arm motor control and leg motor control as well as spasticity, dysphagia, aphasia, and neglect, functional improvements have been documented after rTMS interventions. Further examples are motor deficits in Parkinson's disease, impaired gait and spasticity in incomplete spinal cord injury (SCI) subjects, and other frequently encountered clinical conditions such as tinnitus and neuropathic pain.

This book provides a state-of-the-art overview to what extent rTMS applications can therapeutically be considered in these areas of clinical neurology, pinpointing both to the encouraging clinical evidence available so far and the limitations of our

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knowledge asking for caution with regard to introducing rTMS interventions into routine clinical practice. While clinical benefits have at times been impressing, many questions still remain unanswered.

The aim of this chapter is to reflect some of the methodological and clinical reasoning that can be deduced from the evidence portrayed in this book and to address some of the questions that need further attention before rTMS interventions can be introduced in clinical practice in a more widespread manner.

12.2 Issues to be Considered for Scientific and Clinical Reasoning

12.2.1 Response Variability

For clinical decision-making, the variability of the brain's response and any behavioral effects to rTMS applications cause the problem that it is difficult to predict any individual's response.

One reason for the observed variability might be that TMS impulses activate many different synapses, both of excitatory and inhibitory neurons in the cortex (Di Lazzaro and Rothwell 2014). Further, rTMS can affect learning processes in a facilitatory way or as suppression. Different functional networks might again respond differently to comparable rTMS interventions. Age, gender, time of day, physical activity, prior history of synaptic activity, and genetics have all been shown to account for the variability responses to TMS impulses of the cortex (Ridding and Ziemann 2010).

One way to deal with the fact of intersubject variability is to test the effects of different rTMS approaches in single subjects and only then to engage in a series of applications for the individually most effective approach. The selection could both be based on individual behavioral data and individual neurophysiological data such as motor evoked potentials (MEP) or TMS-induced EEG changes, i.e., transcranial evoked potentials (TEP) (Premoli et al. 2014).

The infinite variability of the stimulation options (pulse waveform, frequency, intensity, number of stimuli, pattern of stimuli, schedule of repeated applications, site of application, type of coils used and its orientation, and any combinations of rTMS applications simultaneously or consecutively) adds to the variability of results across trials. As an example, in neuropathic pain rTMS applications over the primary motor cortex contralateral to the affected body side worked best with high-frequency (10 Hz) but not low-frequency (e.g., 0.5 or 1 Hz) rTMS (Lefaucheur et al. 2001a) and better when intensities used had been below motor threshold.

Further, the selection of physiological brain imaging and/or behavioral outcome measures influence results and type of information that can be deduced from individual studies or meta-analyses.

There is thus a need to describe meticulously and standardize both stimulation and assessment protocols across trials, to document potential modifiers, and to conduct confirmative large multicenter trials with subgroup analyses (only) for approaches with a marked clinical benefit in smaller trials.

12.2.2 Models of Therapeutic Action

12.2.2.1 Motor Rehabilitation After Stroke

Comparing cerebral activation pattern when performing movements with either the paretic or non-paretic hand in patients with unilateral stroke frequently documented a higher bilateral and thus contralesional activity when the paretic hand was moved compared to a more contralateral and lateralized activation pattern with movements of the non-paretic hand (e.g., Grefkes et al. 2008). Two mechanisms have been suggested as explanation for this "overactivity" of the contralesional motor network representing both (a) an adaptive and (b) maladaptive mechanism of functional reorganization. Further, a time-dependent role of the contralesional motor activity has been proposed, with a supportive influence early after stroke that declines with time (Grefkes and Ward 2014). According to a "vicariation model," (a) homologue sensorimotor areas of the contralesional side can support motor functions that have been lost by damage to the ipsilesional network as an adaptive mechanism of functional reorganization; conversely, in the model of "unbalanced interhemispheric inhibition (IHI)," (b) a net inhibition of the lesioned motor network exerted by the non-lesioned hemisphere acts as a maladaptive influence poststroke and impairs functional recovery. To the extent that such an unbalanced IHI from the contralesional M1 to the ipsilesional M1 exists, both an inhibitory rTMS to the contralesional M1 and an excitatory rTMS to the ipsilesional M1 are treatment options to counterbalance this maladaptive influence (Volz et al. 2015).

While the interhemispheric competition model has explanatory value for rTMS effects that have been observed in motor stroke, it must be kept in mind that the two models that both receive some experimental credit (i.e., the vicariation model and the interhemispheric competition model) would predict opposite effects by rTMS interventions. It remains to be determined for which patient and point in time poststroke the interhemispheric competition model is a valid assumption for rTMS interventions targeting the ipsilesional or contralesional M1.

12.2.2.2 Aphasia After Stroke

Language is represented in distributed brain networks frequently with left hemisphere dominance. Recovery from damage to parts of the network depends on the adaption in the undamaged brain. Functional imaging techniques document activation pattern that is associated with language processing. In recovering from aphasia after stroke, the observed pattern depends on the site and extent of the stroke, and they change over time as does the course of recovery (Heiss et al. 1999): with small lesions outside the primary centers, the original activity pattern is restored and clinically optimal recovery can be observed; with moderate damage to the primary centers, interhemispheric compensation with changes in activation pattern is associated with good recovery; with severe damage to primary centers, reduction of transcallosal inhibition is thought to cause activation of contralateral homotopic areas associated with less efficient recovery of function. Conversely, contralateral homotopic areas might be limiting the functional activity and thereby recovery by their transcallosal inhibition of primary centers.

An intervention that reduces excitability of the contralesional Broca's homologue area by LF rTMS might facilitate the reactivation of primary centers including Broca's area and thereby enhance the potential of speech and language therapy (Naeser et al. 2011). This has specifically been shown by Thiel and coauthors (2013): although only one stimulation site was tested in patients with different types of aphasia, the intervention group experienced a more pronounced language improvement than the sham group. The rTMS-induced inhibition of overactivation in homotopic speech areas of the contralesional hemisphere and the shift of activation back to the dominant hemisphere were associated with significant improvement of the language function in the group treated with rTMS combined with speech and language therapy.

Here we have an example where rTMS at one stimulation site (Broca's homologue) could induce a shift of network activation back from the nondominant to the dominant hemisphere and where this shift was associated with functional/behavioral recovery of a complex function such as language, even though the type of language deficits (aphasia syndromes) and the patients' lesion sites were different. Larger trials with subgroup analyses would be necessary to learn whether a "one site for all" rTMS target would be a valid model for rTMS interventions in aphasia after stroke. Nevertheless, the experiment shows the potential to intervene and modify recovery of network activities targeting one strategic stimulation site. The coupling of rTMS with speech and language therapy points to a priming role of rTMS in aphasia therapy.

12.2.2.3 Neglect After Stroke

According to Kinsbourne's "opponent processor model," each hemisphere causes a natural attention bias to the contralateral hemifield (Kinsbourne 1977). Under normal conditions, the two hemispheres are kept in balance due to interhemispheric inhibition. In spatial neglect patients, damage to either hemisphere leaves the contralesional intact hemisphere unopposed. As a result of this reduced inhibition, the contralesional hemisphere becomes overactivated and causes an ipsilesional attention bias.

When the posterior parietal cortex (PPC) has been used as rTMS stimulation site, both inhibitory rTMS protocols to the left non-lesioned hemisphere (Cazzoli et al. 2012; Kim et al. 2013) and an excitatory rTMS protocol to the right lesioned hemisphere (Kim et al. 2013) produced functional improvements of neglect symptoms with benefits in everyday life situations in patients with right hemisphere stroke suffering from neglect. Here again, there is an example where stroke-related functional deficits could be ameliorated by rTMS. More specifically, assuming that an unbalanced IHI from the contralesional PPC to the ipsilesional PPC exists, both an inhibitory rTMS to the contralesional PPC and an excitatory rTMS to the ipsilesional PPC were treatment options to counterbalance this maladaptive influence in stroke patients with neglect.

12.2.2.4 Dysphagia After Stroke

Dysphagia after stroke is a condition where a bilaterally organized sensorimotor system is affected. Dysphagia can result from a unilateral or bilateral hemispheric

stroke or a brainstem stroke. In hemispheric stroke, it seems most severe when the "dominant" swallowing hemisphere is affected (Hamdy et al. 1997), and recovery from dysphagia after hemispheric stroke is associated with an increase of the pharyngeal cortical map in the unaffected hemisphere (Hamdy et al. 1998).

A consequence of this observation for rTMS applications could be to use an rTMS intervention that increases excitability of the pharyngeal motor cortex in the contralesional hemisphere. This would be the opposite to the most frequently used approach in arm motor, aphasia, and neglect rehabilitation after stroke, where excitability-reducing low-frequency rTMS has successfully been applied to the contralesional hemisphere or excitability-increasing high-frequency rTMS to the affected hemisphere's M1. And yet, HF (5 Hz) rTMS over the contralesional pharyngeal motor cortex for 10 min per day for 2 weeks improved dysphagia in subacute dysphagic stroke patients; the effects were corroborated at a 2-week follow-up (Park et al. 2013). Thus, we have an example where the opposite approach (enhancing excitability in the contralesional motor cortex) to the conventional approach in motor, language, and neglect rehabilitation produced a clear and prolonged clinical benefit.

A parallel observation had been made in gait rehabilitation after stroke. In a sham-controlled RCT with crossover design, positive effects of high-frequency rTMS delivered with a H-coil to both leg motor cortices on lower limb motor function had been documented in chronic ambulatory middle cerebral artery (MCA) stroke patients (Chieffo et al. 2014).

Accordingly, the clinical model for rTMS applications needs to take the basic organization of the treated system into account. It seems unlikely that even for a condition such as stroke, different target symptoms would all be manageable by the same logic. To the contrary, any rTMS approach and the presumed model of action need to be defined and experimentally tested for each condition treated.

12.2.2.5 Parkinson's Disease (PD)

Motor symptoms are a cardinal feature of PD that to some extent can be positively influenced by rTMS interventions: high-frequency (HF) rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1 rTMS) or over the dorsolateral prefrontal cortex (DLPFC) and low-frequency (LF) rTMS over the supplementary motor area (SMA) have been shown to result in some clinical benefits (see Chap. 9 for details). There were, however, considerable inconsistencies across trials. LF (1 Hz) rTMS of the SMA with a weekly schedule for 8 weeks was among the more favorable rTMS interventions for the treatment of motor symptoms in PD (Shirota et al. 2013).

Thus, the issue of selecting a target site for the treatment of motor symptoms in PD cannot be regarded as solved. It is, however, noteworthy that not only primary motor areas can be rTMS targets in the motor domain but other nodes of the motor network such as the SMA or even areas outside the motor network, e.g., the DLPFC. The mode of action here is not clear. A potential role of an overactive SMA-subthalamic nucleus network in PD had been entertained (Mure et al. 2012). Motor effects following DLPFC stimulation in PD subjects might (in part) be secondary effects due to its antidepressive action.

Given the complex nature of brain networks involved in various functions such as sensorimotor functions, it follows that a variety of target sites can (or must) be entertained for each condition treated. Models of therapeutic rTMS applications don't have to be restricted to the sites that have been used as targets so far. Rather, the pathophysiology of each condition and the resulting changes in network activities should be taken into account.

12.2.2.6 Neuropathic Pain

Neuropathic pain of either peripheral or central origin has been shown to be reduced after cortical rTMS applications. Most frequently, the primary motor cortex contralateral to the affected limb or side of the face has been treated.

These rTMS applications over the primary motor cortex contralateral to the affected body side worked best with high-frequency (10 Hz) but not low-frequency (e.g., 0.5 or 1 Hz) rTMS (Lefaucheur et al. 2001a) and better with intensities below motor threshold. In addition, focal rather than non-focal (Rollnik et al. 2002) stimulation induced clinical benefits. And, rTMS was more effective when the target was adjacent to the cortical presentation of the affected limb rather than within its center (Lefaucheur et al. 2006) and bigger with rTMS over M1 as compared to S1, premotor, and supplementary motor area (Hirayama et al. 2006), a reason why neuronavigated rTMS could be beneficial for this condition. Further, the maximal clinical effect has been observed to be delayed by 2–4 days after single rTMS sessions (Lefaucheur et al. 2001b). Yet, single sessions are not sufficient to induce a lasting clinical effect while a series of 5–10 daily sessions are and then might need maintenance sessions for adequate long-term pain relief (Hodaj et al. 2015).

Thus, increasing excitability in the primary motor cortex adjacent to the representation of the affected body part by HF rTMS, and doing so repeatedly over days, possible with long-term maintenance sessions induces changes in the brain that are associated with a clinically relevant analgesic effect in patients with neuropathic pain. The connections of the primary motor cortex seem to be critically involved in this effect. The rTMS target outside and adjacent to the representation of the body part affected by neuropathic pain points to the relevance of cortical body representations for this therapeutic intervention.

12.2.2.7 Tinnitus

The pivotal question "which is the target site for clinical rTMS applications?" needs to be addressed for all conditions treated. The need for such a clarification can further be exemplified by rTMS approaches to tinnitus.

Tinnitus is a complex psychophysical phenomenon. Aside from the acoustic phenomenon (i.e., the perception of a tone), it is further characterized by attentional (degree of awareness of a tinnitus), emotional (degree of distress), and memory aspects. Accordingly, the neurobiology of tinnitus is associated with combined network activations in auditory perceptual, saliency, emotion/distress, and memory networks (De Ridder et al. 2011).

Here, it is evident that there would be a multitude of potential stimulation sites to treat aspects of the tinnitus phenomenon, its neural establishment, its emotional connotation, and its course over time.

Quite a few smaller and medium-sized RCTs assessed the clinical efficacy of rTMS applications in tinnitus and, while not without inconsistencies across trials, overall documented some clinical benefit (Meng et al. 2011).

LF (1 Hz) rTMS as trains of 1200–2000 pulses repeated over 5–10 days unilaterally and applied to temporal or temporoparietal cortical areas, either on the left side or contralateral to the perceived tinnitus, have most frequently been used and produced clinical benefits, partially long term. It was assumed that this rTMS approach can interact with an abnormal hyperactivity of auditory cortices that may constitute the neural correlate of tinnitus perception.

The considerable variability of study results does, however, question whether these approaches can yet be considered for routine clinical practice (Langguth and De Ridder 2013).

Even such basic issues as high- versus low-frequency rTMS are open to debate: two RCTs showed that 10 Hz and 25 Hz rTMS are at least as efficacious as 1 Hz rTMS for tinnitus treatment (Khedr et al. 2008; 2009, 2010).

Given the widespread network characteristics of neural correlates of tinnitus, it is well conceivable that a combined modulation of both frontal and temporal cortex activity might improve rTMS effects in tinnitus patients as shown for a combination of 1 Hz left temporal rTMS preceded by a 1 Hz right prefrontal rTMS (Kreuzer et al. 2011).

Regarding the complex psychophysical nature of tinnitus, observations that the degree of reduction of tinnitus achieved with rTMS therapy can be associated with a decrease of emotional distress (e.g., anxiety and depression) (Khedr et al. 2010) are promising. They indicate that a secondary emotional distress can be ameliorated by targeting the primary perceptual dysfunction.

Overall, the situation for rTMS applications in tinnitus is, however, not yet satisfying. The limited clinical research performed so far (especially RCTs) and the complexity of the psychophysical phenomenon all make it difficult to base clinical recommendations on our current rTMS knowledge base. While the future might provide us with more refined and potentially more robust treatment effects in tinnitus, the current status can be regarded as a first valuable step toward a clinically useful therapy for a condition with little substantial, neurobiologically based therapeutic options of proven effectiveness. It is fair to state that rTMS therapy for tinnitus can be considered on an individual basis embedded in a comprehensive tinnitus management strategy (Langguth et al. 2015).

12.2.3 Schedule of rTMS Applications

For clinical purposes, achieving effects of rTMS that last for a period of time if not enduring is pivotal for its usefulness. The clinical applications so far have all

included multiple, i.e., a series of rTMS interventions across a specified span of time. Yet, the specific schedules could hardly be more divergent.

Most clinical trials in motor rehabilitation after stroke applied ten daily rTMS sessions over a 2-week course, some up to 20 daily sessions in 4 weeks. Similarly, daily rTMS sessions have been given mostly for 2 weeks in aphasia and for 1–2 weeks in dysphagia and tinnitus (here up to 4 weeks). Given the variety of protocols applied and the results obtained, it is not possible to draw firm conclusions about the optimal schedule for each condition assessed.

It is, however, noteworthy that in motor stroke, 4 weeks of rTMS treatments achieved considerably bigger improvements than 2 weeks (Sung et al. 2013; Wang et al. 2014). It is conceivable that in a situation where cerebral representations need to be reestablished over many weeks through repetitive training structures as in arm paresis after stroke, a prolonged rTMS treatment schedule can modify and strengthen the accumulating effects of practice.

The situation has been different in neglect therapy after stroke and Parkinson's disease (PD) subjects.

While in neglect therapy conventional schedules with a single session per day for a course of 2 weeks had also been applied, shorter schedules, i.e., two sessions per day on 2 consecutive days with a modified continuous theta burst stimulation (mod. cTBS), have been shown to be successful (e.g., Cazzoli et al. 2012). Importantly, lasting effects with improvement in everyday life activities were observed with this approach. It might be that in a condition such as neglect, the assumed unbalanced interhemispheric inhibition (IHI) can substantially be modified with a restricted rTMS intervention (e.g., over 2 days) and that balancing IHI in this way produces in itself a lasting beneficial clinical effect that does not require the combined effect of repeated rTMS priming and practice for reestablishing cerebral representations.

In PD, we are faced with a chronic degenerative condition where the CNS has to the extent possible been involved in compensating functional loss. Here, we do not have an acute damage of the brain that leads to reorganization but rather a fairly stable yet slowly deteriorating nervous system. Shirota et al. (2013) tested a weekly rTMS over the supplementary motor area (SMA) as either LF (1 Hz), HF (10 Hz), or sham stimulation over a total of 8 weeks in subjects with PD. Only the LF rTMS improved the motor symptoms compared to the sham group. The beneficial effect of the 1 Hz rTMS intervention lasted at least 12 weeks after the end of the treatment. In a situation with a chronic motor deficit, such an extensive treatment schedule, i.e., weekly spaced, could therefore be a clinical effective approach leading to some "lasting" effects.

In another chronic condition, i.e., neuropathic pain, the maximal analgesic effect of a single HF (10 Hz) rTMS session over the primary motor cortex contralateral to the body part affected was delayed by 2–4 days (Lefaucheur et al. 2001b) indicating that the mode of action involved rTMS-induced plastic changes in cortical circuits. Further, lasting clinical effect might best be achieved with series of 5–10 daily sessions that are followed by maintenance sessions for adequate long-term symptom control in such a chronic dysfunctional state as in neuropathic pain (Hodaj et al. 2015).

Thus, regarding functional or perceptual outcomes of clinical rTMS, the time course of effects needs to be reflected for each condition treated. Taken together, there might be situations where (a) a maladaptive network situation can be treated with a short cluster of rTMS interventions (e.g., neglect), (b) rTMS is used as regular priming for training-based reorganization over a period of training (e.g., motor control or aphasia after stroke), or (c) influences chronically altered brain networks with more extensive (i.e., more sparsely distributed) rTMS schedules (e.g., neuropathic pain or motor symptoms in PD).

12.2.4 Combinations of rTMS Stimulation

As has been pointed out throughout this book, the clinical effects of individual rTMS interventions are far from being well known and the evidence – while being supportive – is not yet to be considered conclusive. And yet, there had been instances where combinations of rTMS interventions had been tested clinically. Examples of results of these investigations are worthwhile considering.

Combinations had been used (a) at single stimulation sites within stimulations sessions, (b) at different stimulation sites within sessions, and (c) across stimulation sites for consecutive series of stimulation.

Gillick et al. (2014) investigated a 6 Hz primed low-frequency (1 Hz) rTMS intervention in the contralesional hemisphere targeting M1 with a modified constraint-induced movement therapy (mCIMT) program in children with congenital hemiparesis. By enhancing the excitatory level of the cortex by a first HF 6 Hz rTMS, a paradoxical effect of enhanced immediately subsequent inhibition by LF 1 Hz rTMS was intended. In this small RCT with 20 children, primed, low-frequency rTMS combined with CIMT appeared to be safe, feasible, and compared to the sham rTMS/CIMT group efficacious in pediatric hemiparesis.

Khedr et al. (2014) evaluated the long-term efficacy of dual-hemisphere rTMS on poststroke aphasia. Each patient received LF 1 Hz rTMS over the right unaffected Broca's homologue area first and then HF 20 Hz rTMS over the left affected Broca's area for 10 consecutive days followed by speech/language training. In this study, the authors documented bigger language improvements after real rTMS compared to sham rTMS, which remained significant 2 months after the end of the treatment sessions.

rTMS combinations across stimulation sites for consecutive series of stimulation for motor recovery after stroke had been applied and tested in two RCTs from Taiwan (Sung et al. 2013; Wang et al. 2014) where a substantial number of stroke patients received combined rTMS and PT sessions over a total of 4 weeks. The prolonged combination of rTMS with ten daily sessions of contralesional 1 Hz rTMS followed by ten daily sessions of ipsilesional M1 iTBS (intermittent theta burst stimulation) led to the best observed, substantial, and long-term motor recovery (50–70 % improvement compared to the reverse order with 20–30 % and <10 % in the sham-only control group). These results suggest that a prolonged priming of

arm training with both a course of contralesional inhibitory and then ipsilesional excitatory rTMS might enhance motor recovery in subacute stroke patients.

The first two examples provide evidence for the efficacy of within session combinations compared to sham but not in comparison to an individual uncombined rTMS approach. The latter example provides evidence for a superior efficacy of a sequential combination of rTMS approaches compared to both the reverse order and sham. While it is felt that it might be early to assess such combinations when effects of individual rTMS approaches are yet to be determined, it is of course much more informative when the study design enables the critical appraisal not only of a combined treatment versus sham but against their components as well.

12.2.5 rTMS and Training

Given the fact that the brain is constantly involved in use-dependent plasticity and our everyday activities in perceptual and motor behavior as well as cognitive and emotional domains are all linked to such changes in the brain, the distinction between rTMS therapy with and without use- or training-dependent changes is to some extent arbitrary. Yet, there are clinical conditions where the primary therapeutic intention is symptom control and other conditions where the establishment of functional cerebral representations (i.e., learning and/or functional reorganization) is a key issue. Therefore, while not being an exclusive reasoning, it seems plausible to explicitly combine rTMS applications with specific training in the latter instance while such a combination might not be essential for symptom control.

So far, examples for rTMS and symptom control are neuropathic pain, tinnitus, motor deficits in PD, dysphagia, and neglect after stroke. This is not to say that in these conditions effects of rTMS could not be enhanced by specific training procedures but rather are a reflection of the fact that clinical benefits were achieved by rTMS applications without specific linked training procedures.

In motor and language rehabilitation after stroke, when representations for motor and language functions need to be reestablished by repetitive specific training schedules in the affected domains, rTMS therapy has frequently been used as priming with the intentions to enhance the effects of a consecutively following training. Direct proof of this concept has been provided in a paper by Avenanti et al. (2012) indicating that rTMS acts as a priming procedure and enhances training-induced motor recovery when applied immediately before (rather than after) training.

12.3 Concluding Remarks

Much remains to be learned before rTMS applications can routinely be integrated in clinical practice in neurology on a larger scale. Many issues need to be resolved for each condition treated and protocols developed with optimized effectiveness taking individual subject characteristics into account. And yet, the clinical benefits that can be achieved are at times remarkable and favor the clinical application of rTMS

therapy. For example, consider the substantial and long-term arm motor recovery after stroke with a 2-week series of contralesional 1 Hz M1 rTMS followed by 2 weeks ipsilesional iTBS (50–70 % improvement compared to the reverse order with 20–30 % and <10 % in the sham-only control group) (Wang et al. 2014). Comparing 50–70 % improvement to <10 % spontaneous recovery indicates a substantial if not outstanding clinical benefit.

For each condition treated, the body of clinical evidence should be taken into account as well as the recommendations that have been deduced from it. rTMS applications are best provided in centers experienced with the method, accompanied by adequate documentation of stimulation protocol, patient characteristics, and outcomes. Given our need for more evidence to base our clinical decisions on, for the time being rTMS therapy should preferably be applied within clinical trials or observational studies.

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