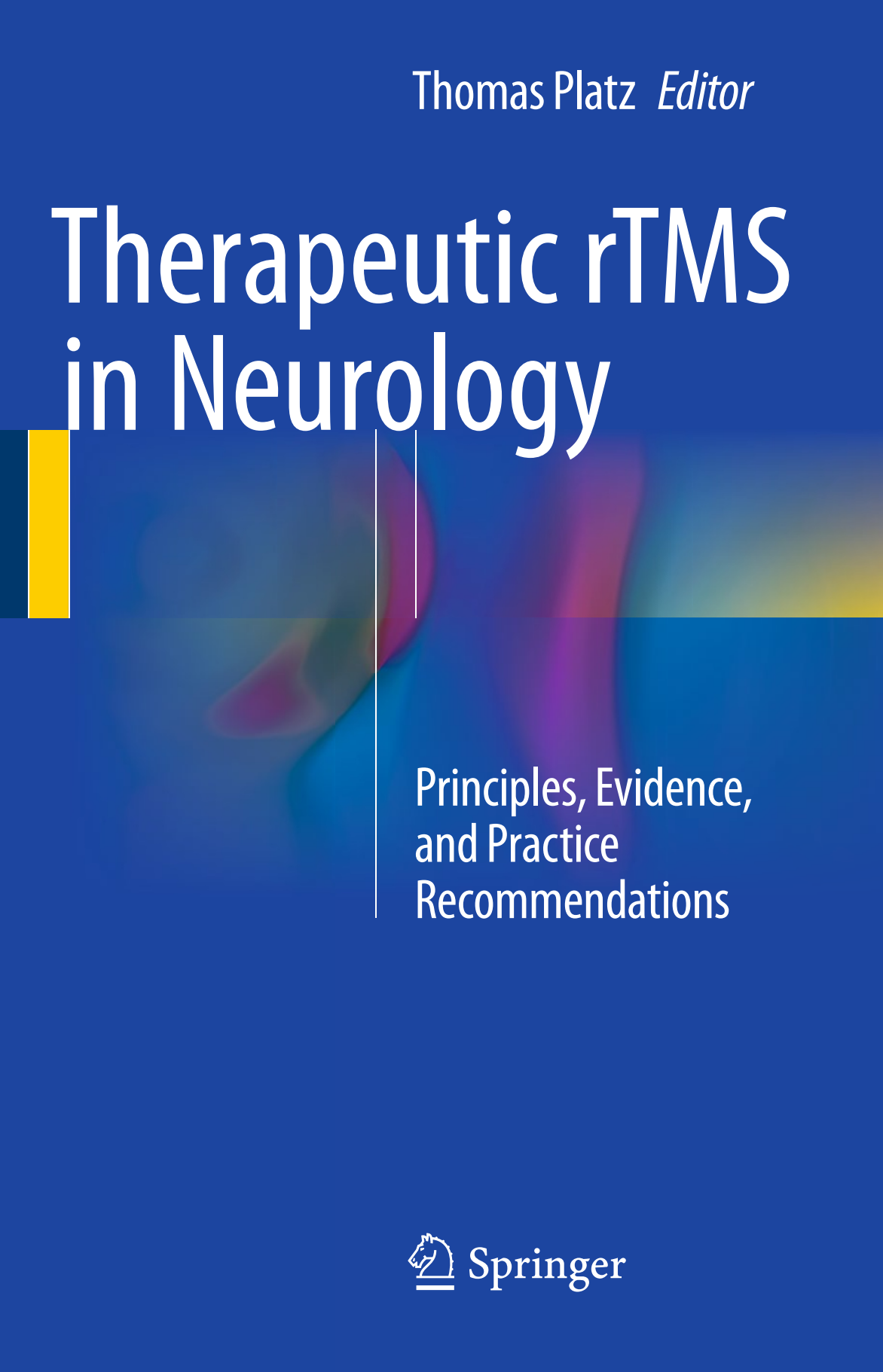
Thomas Platz *Editor*

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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Thomas Platz

Contents

Neurophysiology of rTMS: Important Caveats When Interpreting the Results of Therapeutic Interventions

1

Masashi Hamada and John C. Rothwell

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

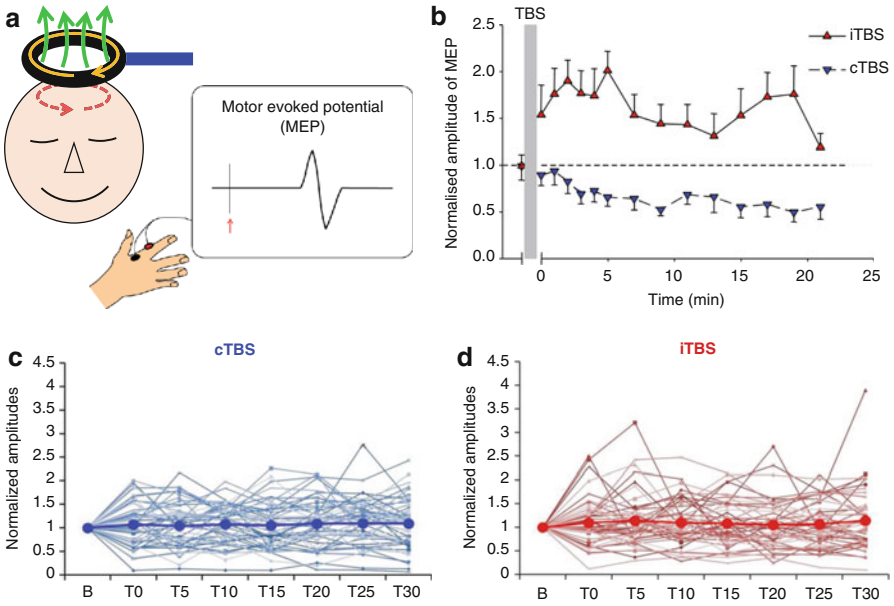

Fig. 1.1 (**a**) Basics of TMS. A large pulse of current in the external stimulating coil generates a rapidly changing magnetic field that rises to, and falls from, 1 T or more within 1 ms, and this field can penetrate the scalp and skull with little impedance. Accordingly, the electrical field it induces 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,

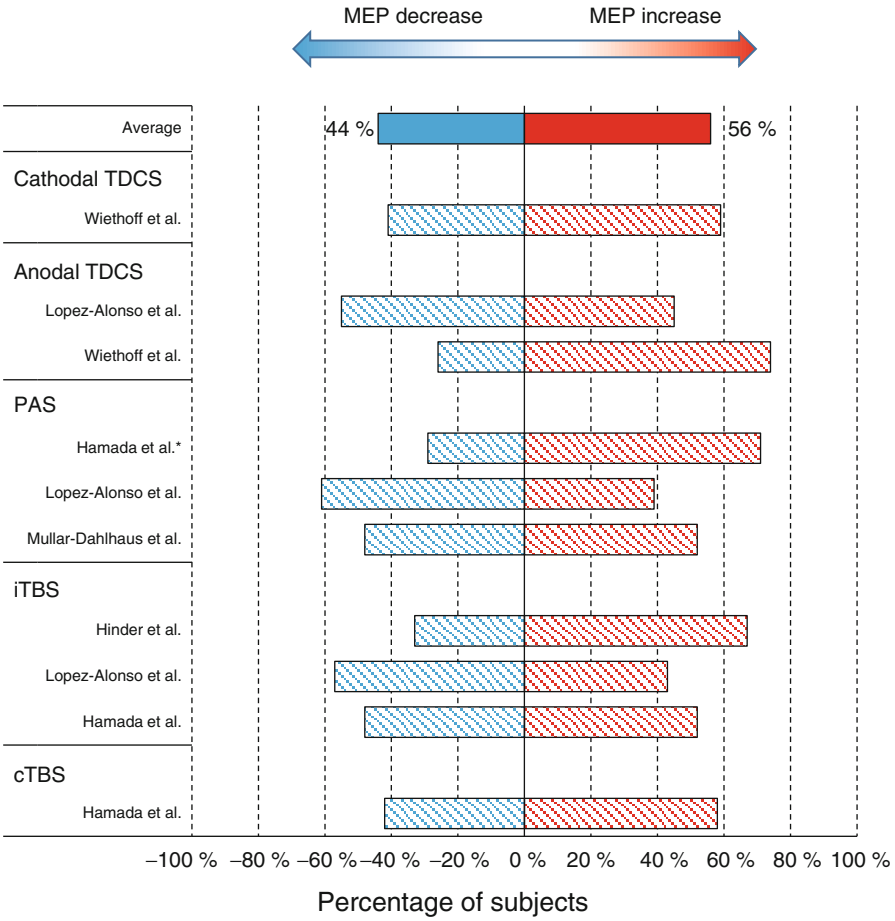

Fig. 1.2 Summary of response profile of each protocol. The bar indicates the percentage of subjects who showed MEP increase or decrease in each study. Note that this is not a meta-analysis and the studies were chosen from recent studies. This is because these include a relatively large number of subjects (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

Maximilian Lenz, Florian Müller-Dahlhaus, and Andreas Vlachos

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

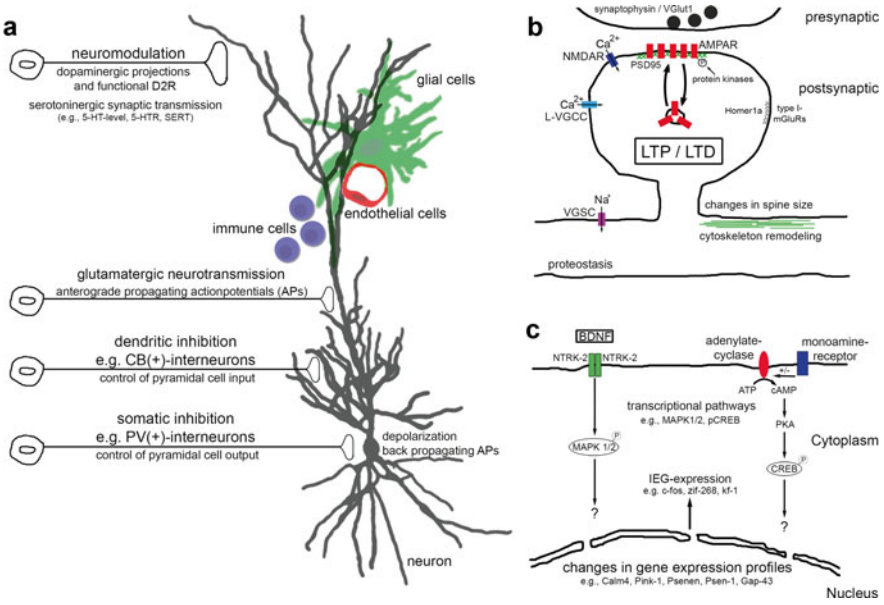

Fig. 2.1 Cellular and molecular effects of repetitive transcranial magnetic stimulation (rTMS) relevant to neural plasticity. (**a**) Schematic illustrating the effects of rTMS on neural tissue. While experimental evidence has been provided that single-pulse TMS can elicit action potentials, the role 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).

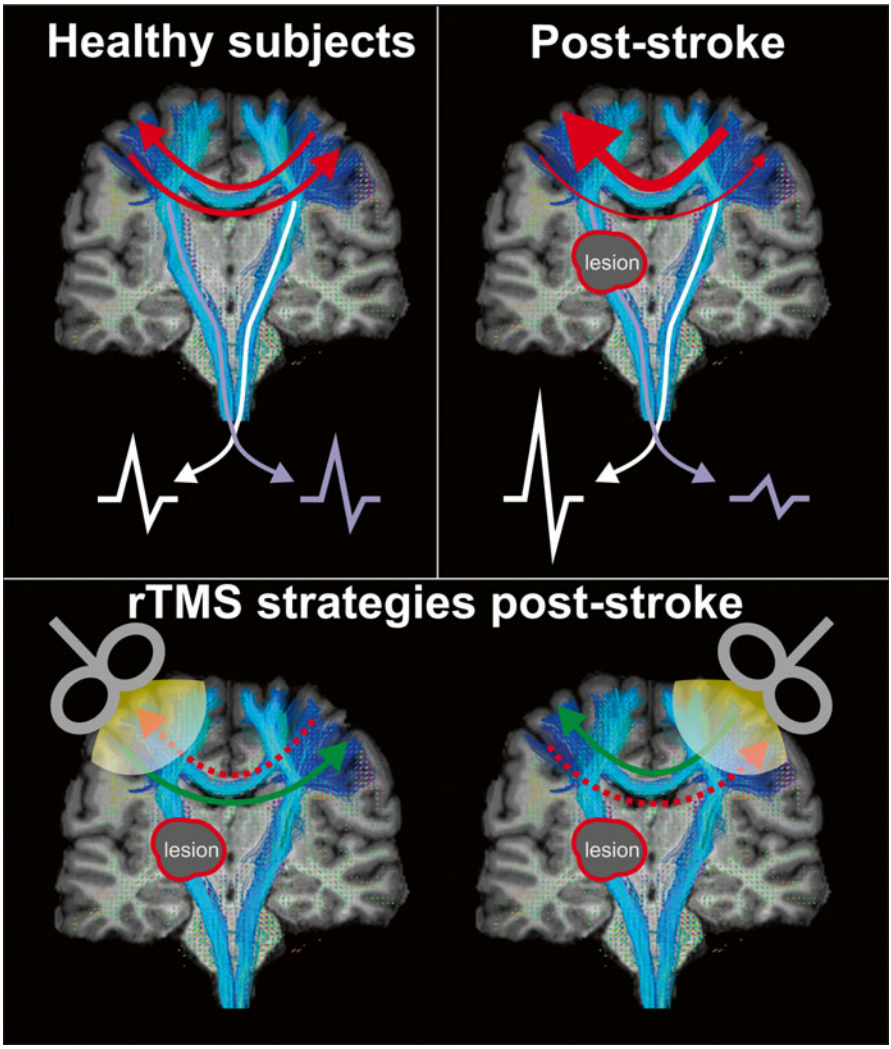

Fig. 3.1 Model of interhemispheric competition: In the healthy brain, interhemispheric inhibition (*red arrows*) is balanced between both M1 at rest, while unilateral movement is associated with a shift toward stronger inhibition of M1 ipsilateral to the moving hand. After stroke, interhemispheric inhibition 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

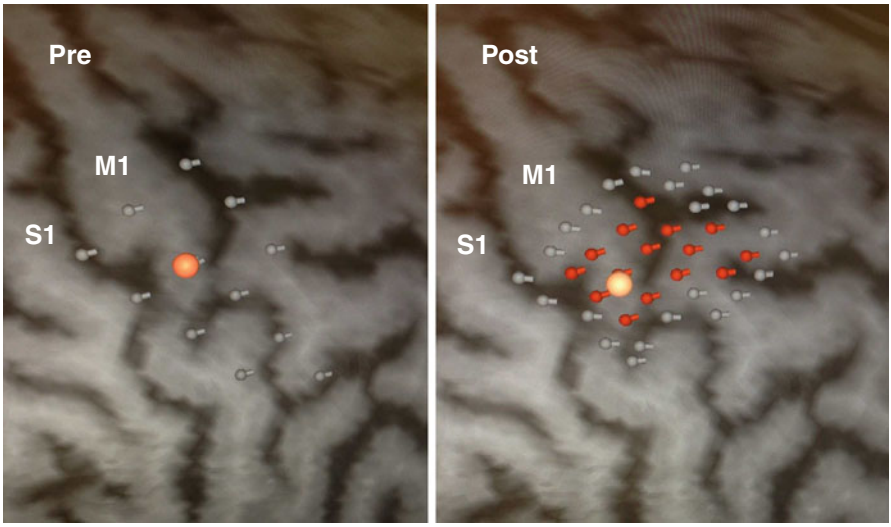

Fig. 4.1 Hand motor cortex mapping before and after a series of contralesional M1 LF 1 Hz rTMS. S1 denotes primary somatosensory cortex. In this case of a 75-year-old female patient, 5.5 weeks post right hemisphere subcortical stroke, mapping of the hand motor areas of the stroke hemisphere was performed 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

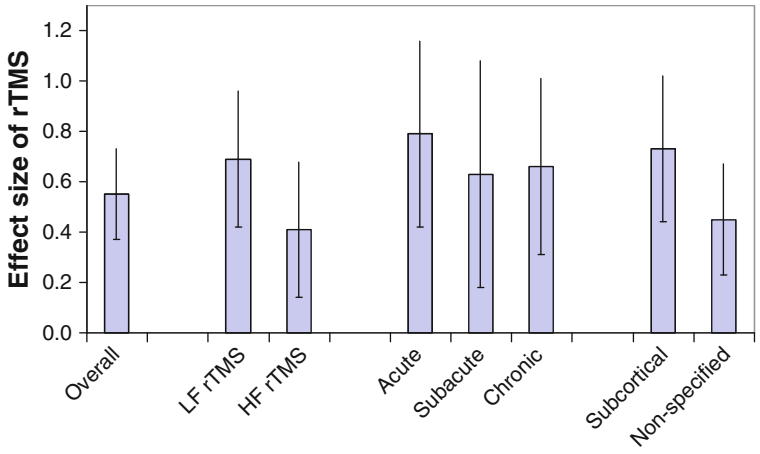

Fig. 4.2 Effect sizes for rTMS in arm motor rehabilitation after stroke according to a meta-analysis by Hsu et al. (2012). Standardised effect sizes and 95 % confidence intervals based on data from 18 trials and 370 patients are presented. Because effect sizes may be influenced by sample sizes and effects 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)

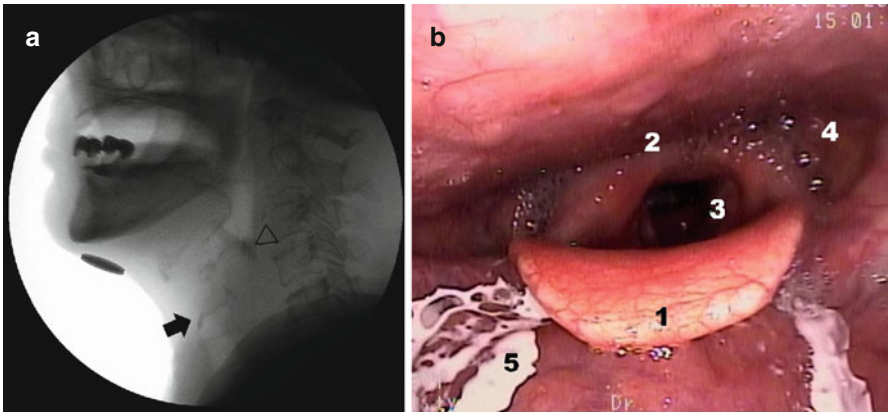

Fig. 5.1 Evaluation tools for swallowing function. (**a**) Videofluoroscopy (VFS). Black arrow shows aspirated barium below the vocal cord and arrowhead shows residue in pyriform sinus. (**b**) Fiberoptic endoscopic evaluation of swallowing (FEES). (1) Epiglottis, (2) esophagus, (3) vocal cord, (4) pyriform 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

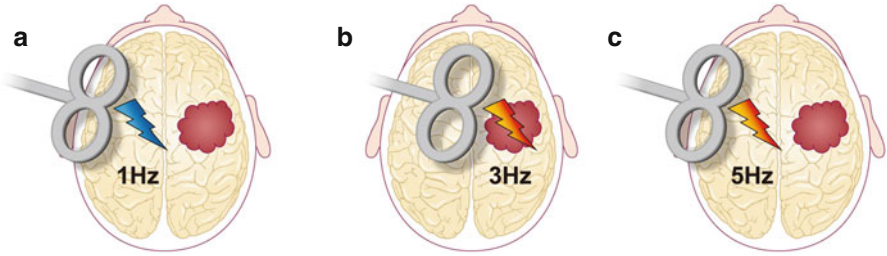

Fig. 5.2 Three different stimulation methods. (**a**) Inhibitory stimulation on contralesional intact motor cortex which makes downregulation of excitability of the motor cortex. (**b**) Excitatory stimulation on ipsilesional affected motor cortex which makes upregulation of excitability of the motor 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

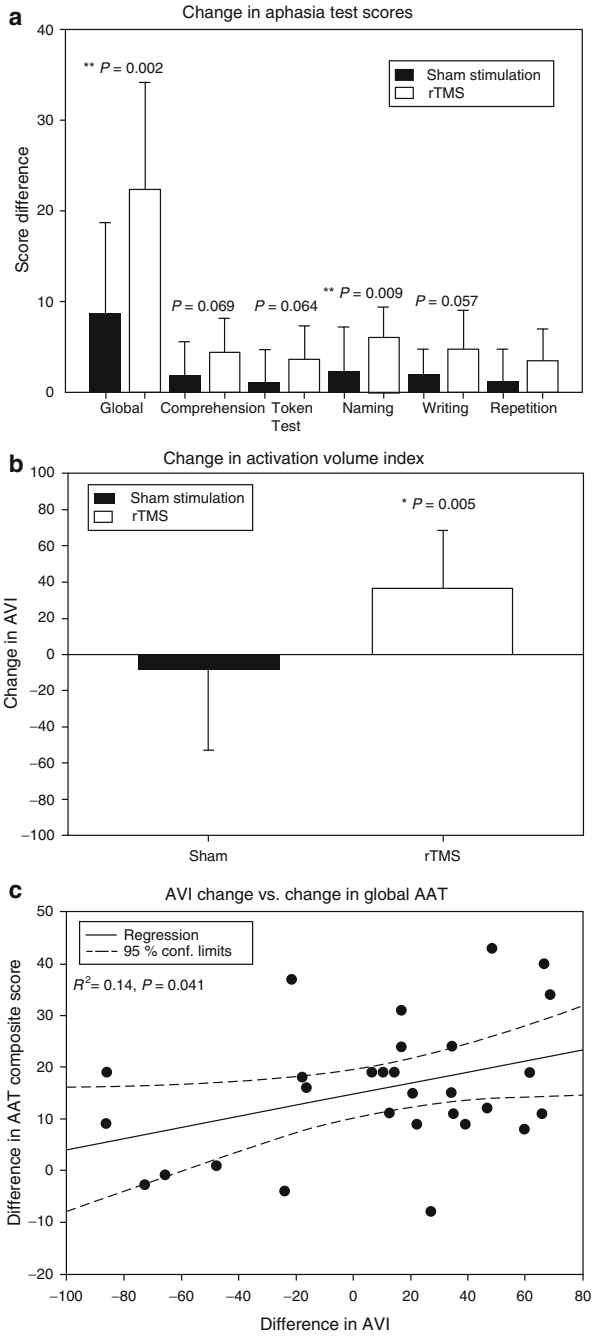

Fig. 6.1 (**a**) (Aphasia score) Change in aphasia test scores pre and post sham or rTMS treatment. There is a significant larger change in global aphasia scores for the TMS group. In the AAT subtest, a significantly larger change for the TMS group was observed in picture naming and trends in the subtests 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

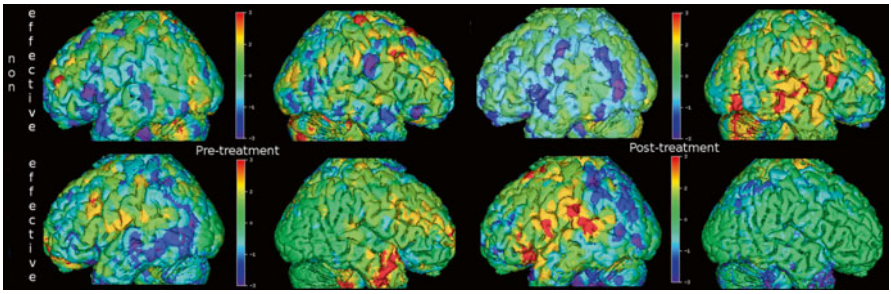

Fig. 6.2 (Effect shift) Language activation PET scans of a sham-treated subject (*top row*) show bilateral activity pretreatment, which consolidates in the right hemisphere after treatment (non-effective shift). In a TMS-treated subject (*bottom row*), the initially bilateral activity shifts to the left 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

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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

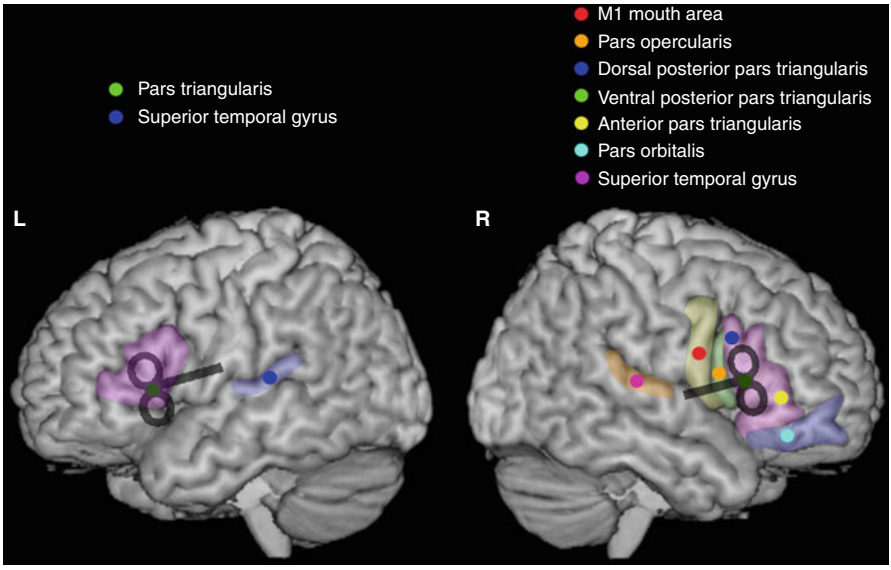

Fig. 7.1 rTMS targets employed in treatment studies of aphasia in the right and left inferior frontal and superior temporal gyri

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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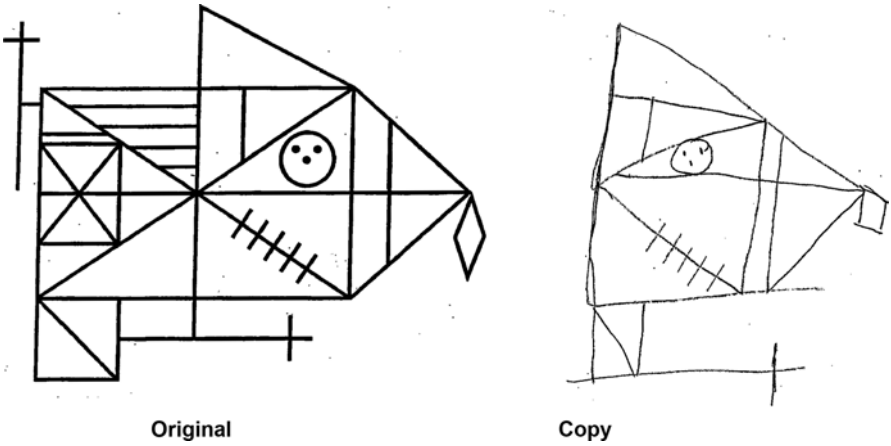

Fig. 8.1 Visual hemineglect in copying Rey figure. The patient largely ignores the *left side* of the figure and copies only parts of the *right side*

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.

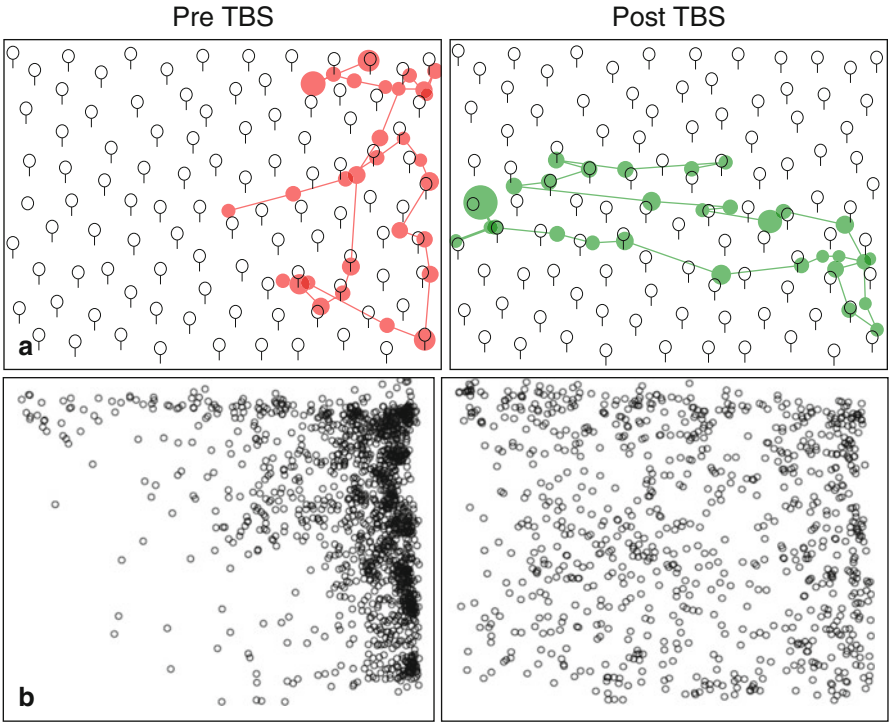

Fig. 8.2 Example of treatment effect with TBS on visual exploration in a search task (own unpublished data). (**a**) *Left side* visual exploration of a patient before TBS treatment. Eye movements (*filled circles*: fixations, lines saccades) were co-registered during the search task. The patient was 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.

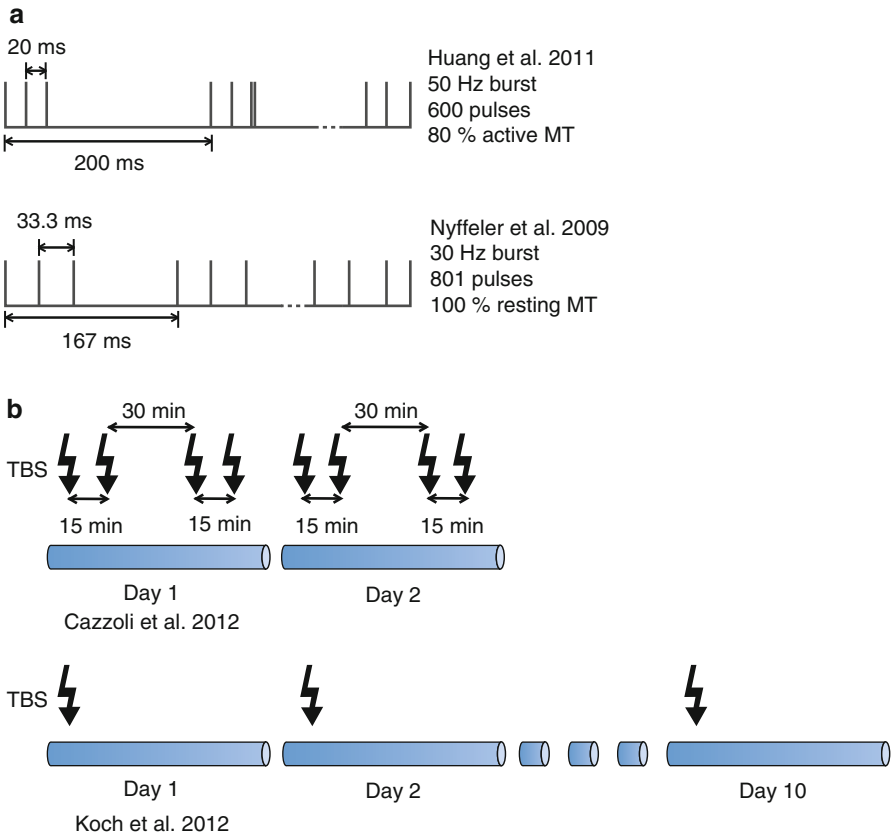

Fig. 8.3 (**a**) Parameters of the two cTBS protocols used in the treatment of visual hemineglect. *Above* the standard protocol according to Huang et al. (2011). *Below* the modified protocol according to Nyffeler et al. (2009). (**b**) Two types of treatment protocols by cTBS. *Above* the protocol 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

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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.

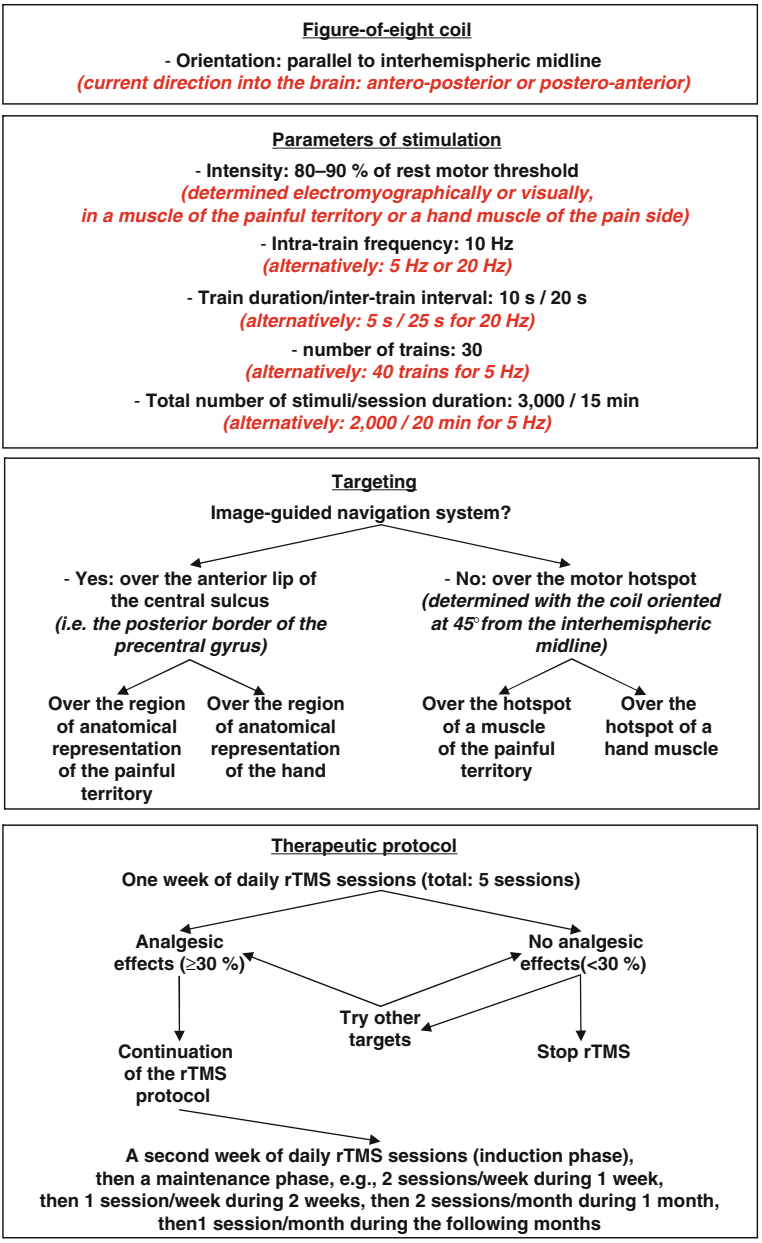

Fig. 10.1 Practical algorithm on the implementation of rTMS in the treatment of neuropathic pain

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).

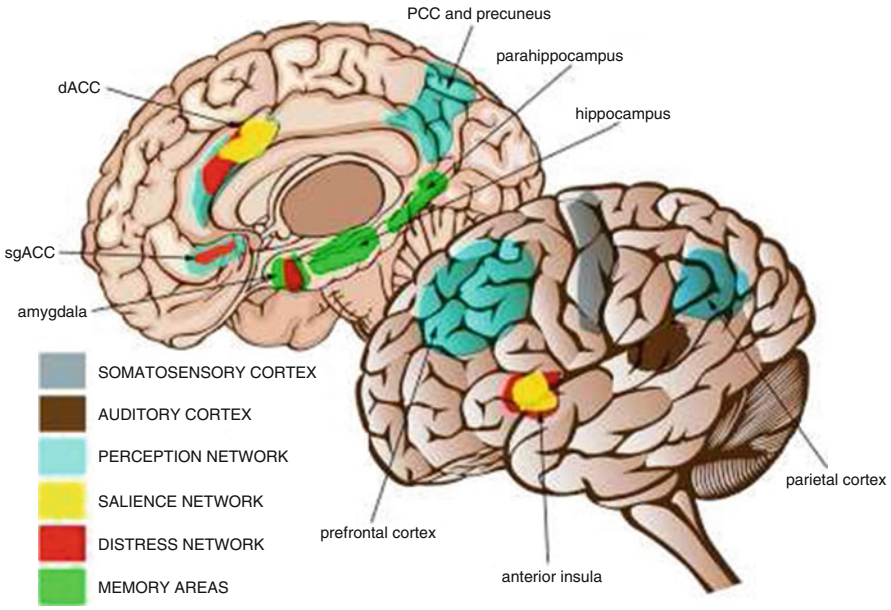

Fig. 11.1 Tinnitus networks. Brain networks involved in phantom perception. Increased activity in the auditory cortex (*brown*) as a consequence of auditory deprivation is necessary, but not sufficient for tinnitus perception. The stimulus becomes consciously aware if auditory activity is connected to 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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