The Mechanism of Action of rTMS

3

3.1 Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of stimulating nerve cells in cortical regions of the brain [1] which can also produce significant therapeutic effects in a number of neurological and psychiatric disorders. However, the mechanisms through which such treatment effects occur is uncertain. Generally speaking, it has been proposed that the effects of high-frequency rTMS in depression occur through an increase of activity in the left DLPFC, which is proposed to be underactive in patients with depression. Low-frequency right-sided rTMS is proposed to reduce right-sided DLPFC activity which is proposed to be overactive in patients with depression. However, rTMS has a complex series of effects on the brain, and research has not necessarily consistently demonstrated these relationships.

In this chapter, we will review the brain mechanisms postulated to be altered by TMS and how they may relate to the treatment of depression.

3.2 Effects of rTMS Assessed in the Motor Cortex

The majority of research into the effects of rTMS has occurred in the motor cortex, where there are easily available means to study alterations in cortical activity. In particular, single and paired pulses of TMS applied to the motor cortex can be utilised to index aspects of cortical excitability and inhibition, providing a ready mechanism to study the effects of repetitive rTMS stimulation. In this regard, rTMS has been shown to result in changes in several physiological parameters in the motor cortex, including in excitability, evidenced in motor threshold (MT) and motor-evoked potential (MEP) alterations; in cortical inhibition and facilitation, evidenced in silent period (SP) and paired pulse inhibition and facilitation (ppTMS) changes; and in alterations in cortical plasticity. These changes appear to be rTMS frequency and intensity dependent.

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3.2.1 Effects on Motor Cortical Excitability

Low-frequency rTMS (1 Hz or less) has been shown to decrease corticospinal excitability (see review in [2]). For example, Chen et al. [3] demonstrated that a 15-min train of suprathreshold 0.9 Hz rTMS applied to the motor cortex reduced MEP size. This reduction lasted at least 15 min after the end of the stimulation train. Siebner et al. [4] found a similar reduction in MEP size in healthy controls, but not in patients with writer's cramp when 1 Hz rTMS was applied over the left primary motor hand area. These findings have been confirmed in more recent studies. Subthreshold 1 Hz stimulation for 4 [5] or 10 [6] min both resulted in significant reduction in MEP size. Muellbacher et al. [7] found that 1 Hz suprathreshold TMS for 15 min increased the motor threshold and reduced MEP amplitude. Notably, the degree of these effects has been shown to be dependent on stimulation parameters such as intensity [8].

Effects of 1 Hz stimulation may also be seen at sites not directly targeted for stimulation. Gerschlager et al. [9] used a considerably lower stimulation intensity than previous studies (90 % active motor threshold (AMT) which approximately corresponds to 60–70 % of resting motor threshold (RMT)). They demonstrated that prolonged 1 Hz stimulation of the premotor cortex, but not the primary motor, parietal or prefrontal cortex, resulted in MEP suppression for at least 15 min. These authors suggest that the effects of premotor cortex stimulation is due to its rich connection to the primary motor cortex and that such stimulation can suppress primary motor cortex excitability even more so than stimulation of the motor cortex itself. Wassermann et al. [10] found that 1 Hz rTMS reduced the excitability of the contralateral, non-stimulated motor cortex as demonstrated by a reduction in the slope of the MEP recruitment curve. Thus, low-frequency stimulation of a cortical area may evoke cortical inhibition in interconnected areas [11]. Reduction of cortical excitability with low-frequency rTMS is clearly relevant to the treatment of depression, with low-frequency stimulation evaluated as an antidepressant strategy when applied to the right DLPFC [12].

High-frequency rTMS appears most likely to have effects opposite to that of low-frequency rTMS and to result in increased motor cortical excitability when applied to the motor cortex (see [2]). For example, Pascual-Leone et al. [13] demonstrated a pattern of facilitation of MEPs produced by a train of rTMS that varied with stimulus intensity and frequency. With 5 Hz rTMS at 150 % RMT, there was clear facilitation of MEPs. At 10 and 20 Hz rTMS with lower intensities (110 % RMT), there was also a consistent pattern of facilitation. In contrast, with 150 % RMT at 10 and 20 Hz rTMS, an alternating pattern of MEP inhibition and facilitation was demonstrated. Several other studies have also demonstrated that MEP size increases with high-frequency rTMS (>1 Hz) [14–16]. Modugno et al. [17] reported that 20 stimuli of 5, 10 and 20 Hz applied to the motor cortex at 100 % RMT resulted in brief MEP suppression that lasted for about 1 s after rTMS. This suppression in the post-train interval was prolonged with longer trains or higher frequencies. Increasing the intensity of the rTMS to 130 and 150 % of RMT resulted in facilitation rather than suppression of the MEP, consistent with previous findings [15]. Therefore, high-frequency rTMS at low intensity may cause inhibition for 1–2 s after the rTMS

train, whereas at higher-intensity, high-frequency rTMS consistently produces facilitation. The mechanisms by which altered excitability occurs in the cortex are unclear. However, it has been suggested that decreased excitability is related to the synaptic process of long-term depression [3], whereas increased excitability has been related to long-term potentiation [18].

The relevance of these studies to understanding the mechanism of action of rTMS in depression is uncertain. Clearly, individual high-frequency rTMS trains applied to the motor cortex increase excitability. However, what is less clear is an understanding of the effects of cumulative stimulation trains over a long treatment session and the accumulation of changes in cortical excitability with daily rTMS sessions over a matter of weeks as is applied in treatment protocols.

3.2.2 Effects on Motor Cortical Inhibition and Facilitation

rTMS can also induce changes in cortical inhibition and facilitation. These changes can be assessed using single- and paired pulse TMS paradigms including (1) short-interval intracortical inhibition (SICI) (i.e. paired pulse TMS (ppTMS) at inhibitory interstimulus intervals (ISIs) of <5 ms) [19], (2) long-interval intracortical inhibition (LICI) [20, 21] and (3) silent period (SP) [22] methods (see Fig. 3.1). These inhibitory paradigms may measure different subtypes of inhibitory GABAergic neurotransmission [23]. Cortical facilitation can be measured using paired pulse TMS with interstimulus intervals between 10 and 20 ms, referred to as intracortical facilitation (ICF) [19]. ICF may be mediated by glutamatergic neurotransmission [24].

3.2.2.1 Silent Period (SP)

The effects of rTMS on the SP have been investigated in several studies examining the effects of pulse number, stimulation frequency and intensity. A silent period is mostly believed to assess activity of the $GABA_B$ receptor. Berardelli et al. [25] demonstrated lengthening of the SP with 3 and 5 Hz rTMS at 110 and 120 % of the RMT. Romeo et al. [26] tested rTMS frequencies of 1, 2, 3, 5, 10 and 15 Hz at intensities just above the RMT. They found that trains delivered at ≥2 Hz resulted in a prolongation of the SP, whereas trains delivered at 1 Hz had no effect. In both studies, the authors suggested that the SP was prolonged because rTMS activated cortical inhibitory interneurons. Fierro et al. [27] explored the effects of 1 and 7 Hz rTMS at intensities of 100, 115 and 130 % of the RMT. They found that 1 Hz rTMS applied to the motor cortex near or above the motor threshold reduced the SP. This was interpreted as a decrease in cortical inhibition. In contrast, 7 Hz rTMS resulted in an inconsistent pattern of smaller and larger values for the SP. The authors concluded that rTMS applied at low 1 Hz frequency decreases the excitability of inhibitory interneurons.

Therefore, it appears the effects of rTMS on the SP are dependent on frequency and intensity of stimulation. High-frequency rTMS (>1 Hz) results in lengthening of the SP, whereas low-frequency rTMS (~1 Hz) results in shortening of the SP. Moreover, at high frequencies, increasing the stimulus intensity results in further lengthening of the SP [28]. For example, frequencies ranging from 1 Hz to priming

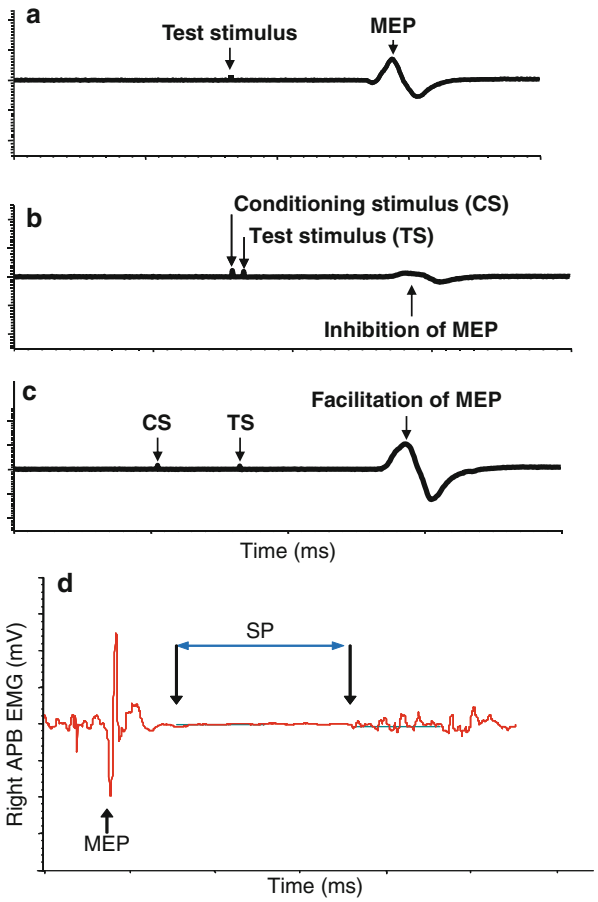

Fig. 3.1 Illustration of the assessment of the measures of short and long intracortical inhibition (SICI and LICI), cortical facilitation (*CF*) and the cortical silent period (*SP*). In the measurement of CF, SICI and LICI, the motor-evoked potential (*MEP*) response to a single test stimulus (**a**) is compared to the MEP response produced by a conditioning and test stimulus (**b**, **c**). When the conditioning stimulus is provided at a very short interval prior to the test stimulus (1–4 ms), the MEP produced is substantially reduced in size (as illustrated in **b**) which is SICI. CF is produced when the interstimulus interval is between 10 and 15 ms and the MEP size is increased over the baseline measure (**c**). LICI is produced when the interstimulus interval is extended to 100 ms (not shown). The SP measure is demonstrated in **d**. The TMS pulse is applied when the corresponding muscle in the contralateral hand is undertaking a tonic muscle contraction. A period of suppression of tonic muscle activity is produced following the MEP, and this is referred to as the silent period

(i.e. 6 Hz followed by 1 Hz), 10 and 20 Hz stimulation resulted in a prolongation of the SP. 20 Hz stimulation resulted in greatest prolongation of the SP. As the silent period was reported to be shortened in depression [29], this finding could help to identify the stimulation parameters needed to optimally treat depression. In fact, treatment with ECT in depression was associated with significant lengthening of the

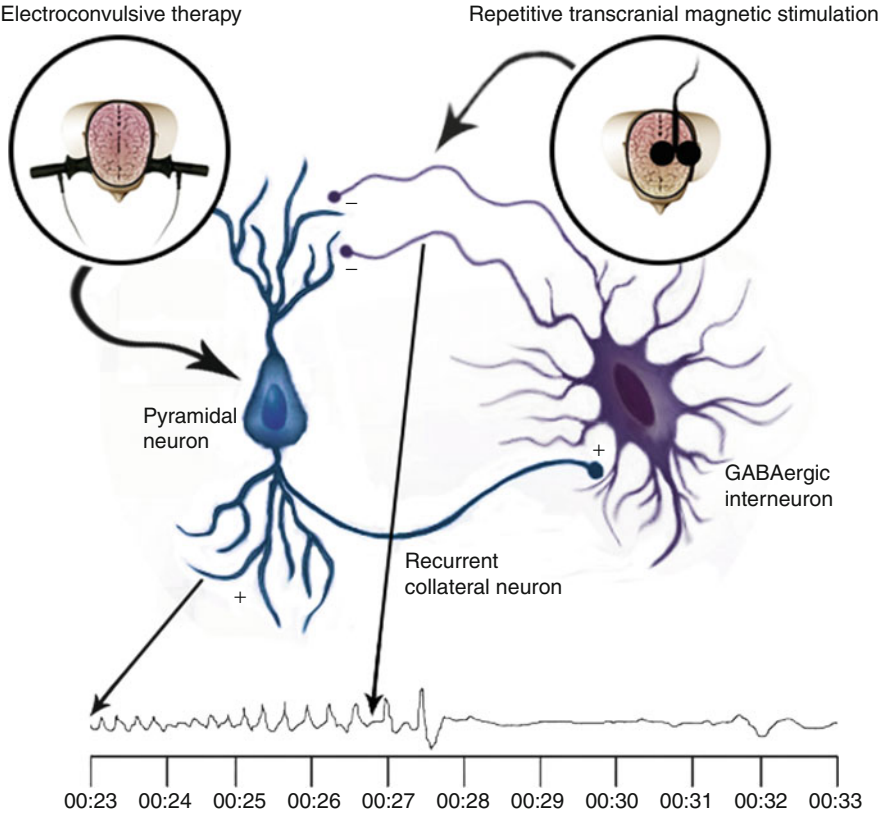

Fig. 3.2 Proposed mechanism for the role of GABAergic potentiation in the treatment of MDD. Cortical stimulation through treatments such as electroconvulsive therapy (ECT) results in rhythmic activation of pyramidal neurons with concurrent spike and wave complexes on electroencephalography (EEG). Subsequently, GABA interneurons are activated via feedback loops which attenuate cortical seizure activity, suppress EEG activity and potentiate GABA inhibitory neurotransmission. Repetitive transcranial magnetic stimulation (rTMS) may exert therapeutic effects by transsynaptic facilitation of GABAergic neurotransmission in an analogous manner

SP [30]. It is possible that both ECT and rTMS share similar mechanisms of action. For example, in Fig. 3.2 we illustrate how ECT induces seizures through direct activation of pyramidal neurons. Seizures terminate, in part, through activation of recurrent collaterals which activate GABAergic interneurons which could account for the SP prolongation seen with ECT. By contrast, rTMS activates interneurons transsynaptically [31], and this could result in a direct effect on GABAergic interneurons without causing a seizure.

3.2.2.2 Paired Pulse Inhibition and Facilitation (ppTMS)

The effects of rTMS on cortical inhibition and facilitation have also been evaluated through ppTMS. SICI assessed with ppTMS is widely believed to assess activity at the $GABA_A$ receptor. Pascual-Leone et al. [32] demonstrated SICI was significantly

reduced with 1,600 subthreshold rTMS stimuli applied at 10 Hz to the motor cortex. In contrast, the same number of subthreshold stimuli applied at 1 Hz had no effect on SICI. Similarly, Peinemann et al. [33] demonstrated that 5 Hz TMS applied to the motor cortex at 90 % RMT caused a significant reduction in SICI but no change in ICF. SICI was significantly reduced after only 30 stimuli of 120 % RMT at 5 Hz [34]. Similarly, SICI was reduced at a stimulation frequency of 15 Hz, whereas ICF was increased. Romero et al. [6] found that subthreshold stimulation with 1 Hz for 10 min significantly decreased ICF, without a concomitant change in SICI. These authors suggest that these effects occur through cortical disfacilitation. As ICF may be associated with activity of excitatory glutamatergic circuits [24], disfacilitation may result in decreased cortical excitation. Therefore, these studies suggest that high-frequency rTMS decreases SICI and, perhaps, increases ICF. Conversely, low-frequency rTMS may decrease ICF without concomitant change in SICI.

The result of this series of studies exploring the effect of rTMS on SP and SICI suggests that rTMS modulates activity at both GABA receptor subtypes.

3.2.3 Effects of rTMS on Motor Cortical Plasticity

Repetitive TMS has also been shown to affect cortical plasticity. In this context, plasticity refers to the reorganisation of the central nervous system (CNS) through changes in internal connections, representational patterns and/or neuronal properties [35]. Ziemann et al. [35] demonstrated that the deafferented motor cortex becomes modifiable by inputs that are normally subthreshold for inducing plastic changes. Their findings suggest that rTMS can modulate plasticity and may potentially be used to enhance cortical plasticity when it is beneficial and suppress it when it is detrimental. In a subsequent study [36], lorazepam (which enhances $GABA_A$ergic neurotransmission) and lamotrigine (which blocks voltage-gated Na^+ and Ca^{2+} channels) were found to abolish the increase in MEP size and decrease in SICI associated with concurrent ischemic nerve block and rTMS to the contralateral motor cortex. Conversely, dextromethorphan (NMDA receptor antagonist) suppressed the changes in SICI but had no effect on MEP. These results provide evidence that the increase in MEP size induced by rTMS and deafferentation involve both GABA-related inhibitory circuits and voltage-gated Na^+ or Ca^{2+} channel-mediated mechanisms. Also, rTMS-induced reduction in SICI appears to involve NMDA receptor activation.

The importance of these motor plasticity findings to the understanding of the mechanisms of rTMS in the treatment of depression is not fully clear. However, depression is a disorder associated with neural mechanisms putatively associated with plasticity impairments. For example, Levinson et al. [29] demonstrated that patients with depression had SP deficits, whilst patients with treatment-resistant depression had both SICI and SP deficits. These findings imply that depression is associated with deficits in GABAergic inhibitory neurotransmission and that more treatment-resistant depression is associated with even more marked GABAergic inhibitory deficits. Further, several dimensions of depressive symptoms (e.g. memory deficits) may be associated with dysfunctional plasticity. Dysfunctional plasticity

may also be a corollary to excessive NMDA receptor activation from chronic stress [37]. Additionally, deficits in brain-derived neurotrophic factor (BDNF) in depression may result in plasticity deficits, as BDNF serves to facilitate plasticity in the brain [38]. It may be possible that one of the mechanisms through which rTMS results in enhanced plasticity is the repetitive stimulation of neurons resulting in synchronous firing and long-term potentiation. That is, by repetitively stimulating neurons, neuronal output is strengthened and, over time, may translate into meaningful and more functional patterns of activity in depression.

3.3 Effects of rTMS Assessed with EEG

Assessment of immediate and direct rTMS-induced alterations in cortical activity cannot only be assessed by electromyography (EMG) methods as described in previous chapters, but also by electroencephalography (EEG). The use of the combination of TMS and EEG methods in the investigation of TMS mechanisms is particularly relevant for studies of working memory (WM) in depression. Abnormalities of WM have been repeatedly found in patients with MDD as well as a range of other psychiatric disorders. As discussed, rTMS over the motor cortex has been shown to enhance Gamma (γ)-aminobutyric acid (GABA)-mediated inhibitory neurotransmission in healthy individuals [28]. Gamma oscillatory activity during higher cognitive tasks is an area of great interest and has recently been shown as a key neurophysiological mechanism underlying WM.

Commonly defined as the ability to maintain and manipulate information over short periods of time [39], WM is often argued as the essence of all prefrontal functions due to its importance in everyday complex cognitive tasks such as language, comprehension, learning and reasoning [40, 41]. Moreover, the dorsolateral prefrontal cortex (DLPFC) is consistently reported to mediate WM processes, revealed through enhanced blood oxygen level-dependent (BOLD) activity in functional magnetic resonance imaging (fMRI) studies [42, 43]. It has been proposed that GABA inhibitory interneurons in the DLPFC contribute to the generation and synchronisation of pyramidal neurons necessary for optimal WM performance [44, 45].

Investigating this issue, we previously conducted a study measuring the effect of 20 Hz rTMS applied to the DLPFC on γ-oscillatory activity across WM load (i.e. 0-, 1- and 2-back conditions) in healthy controls. Active rTMS significantly increased γ-oscillatory activity compared to baseline (pre) and sham stimulation. Moreover, active rTMS caused the greatest change in γ-oscillatory activity in the *n*-back conditions with the greatest cognitive demand, an effect that was limited to frontal brain regions. Finally, active rTMS had no effect on other frequency ranges (i.e. δ, θ, α, β), suggesting a selective effect to oscillatory activity in the γ-frequency range. Collectively, these results suggest that active rTMS applied to DLPFC significantly increased frontal γ-oscillatory activity which was most pronounced at *n*-back conditions of greatest difficulty. Therefore, it is possible that the effects of rTMS on

DLPFC activity in depression may occur through modulation of high-frequency oscillations, and modulation of these oscillations may occur through alterations in the GABAergic neurotransmitter system.

3.4 Neuroimaging Studies of the Effect of rTMS

Part of the allure for studying the motor cortex is that outcome variables can be easily assessed with surface EMG. Exploring non-motor regions, however, requires the combining TMS with other methods of measurement (e.g. EEG, positron emission tomography (PET), near-infrared spectroscopy (NIR) or magnetic resonance imaging (MRI)). A substantial series of studies have utilised brain imaging methods to study either the direct effects of rTMS stimulation (in a variety of cortical regions) or the effects of rTMS treatment in patients with depression.

3.4.1 Imaging of rTMS Effects

Studies directly imaging the effects of rTMS on brain regions have demonstrated that local activation of the cortex results in changes in distributed brain regions. For example, Paus et al. [46] stimulated the frontal eye fields with 10 Hz rTMS at an intensity of 70 % of the maximum stimulator output, whilst PET scans were acquired. They found significant positive correlation with regional cerebral blood flow (rCBF), as measured with ^{15}O-labeled H_2O PET over the same cortical regions, as well as concomitant excitation in the visual cortex of the superior parietal and medial parieto-occipital regions. In an alternative approach, Nahas et al. [47] used 1 Hz rTMS to stimulate the prefrontal cortex, whilst functional MRI (fMRI) scans were conducted. This was done in an effort to measure connectivity and clarify the intensities that are required to produce activation in this cortical region. Previous studies measuring activation in non-motor cortical areas based intensities on those required to produce activation to the motor cortex [48]. Given the cytoarchitectural differences between these regions [49] however, such parameters may not be accurate. As such, the prefrontal cortex was stimulated with a range of intensities (e.g. 80, 100 and 120 % of RMT). Nahas et al.'s results can be summarised into four main findings: (1) greater intensities produced greater local and contralateral activation, (2) stimulation of the left prefrontal cortex resulted in bilateral effects, (3) rTMS of the left prefrontal cortex produced greater activation on the right side than the left side, and (4) stimulating at 80 % of the RMT for 20 s failed to produce significant prefrontal activation.

An additional imaging approach used to study rTMS effects has utilised metabolic imaging with PET. With this method, Strafella et al. [50] demonstrated that rTMS applied to mid-dorsolateral prefrontal cortex resulted in dopamine release in the striatum of the human brain, indicating that rTMS applied to the cortex can induce neurochemical change in subcortical brain regions.

The most relevant conclusions from direct neuroimaging studies of rTMS to understanding the mechanism of action of rTMS treatment of depression are clearly that rTMS produces changes locally and at distant brain sites within connected circuitry. This suggests the possibility that rTMS treatment may work through local effects, distal effects or a combination of both. It is also quite plausible that the mechanism of action of rTMS may involve changing the strength of connections between areas in these brain circuits.

3.4.2 Imaging of rTMS Effects in Depression

Of more direct relevance to understanding the mechanism of action of rTMS treatment in depression are a series of studies that have examined brain activity pre- and post-rTMS treatment. Several existing lines of evidence suggest that MDD is more commonly associated with hypoexcitability over the left prefrontal cortex and/or hyperexcitability over the right prefrontal cortex. The strongest evidence in support of this relates to the much higher rates of depression in patients with left-sided strokes (the anatomic equivalent of hypoexcitability) than in the general population. Moreover, patients with right-sided strokes (the anatomic equivalent of hyperexcitability) experience manic symptoms at much higher rates than in the general population [51].

Imaging studies have also demonstrated that MDD may involve dysregulation of cortical activity, with lower activity in the left dorsolateral prefrontal cortex and higher activity in the right dorsolateral prefrontal cortex [52, 53]. Further, rTMS treatment in MDD has been directly shown to be associated with a normalisation of hypoexcitability over the left prefrontal cortex and normalisation of hyperexcitability over the right hemisphere [54]. This is consistent with the finding that rTMS applied at high frequencies (e.g. 10 Hz) increases excitability in the cortex [55], whilst rTMS applied at low frequencies (e.g. 1 Hz) decreases excitability in the cortex [3]. Specifically, Kimbrell et al. [54] reported that 13 patients with depression responded differently to 1 Hz versus 20 Hz rTMS. There was a significant negative correlation between change in HAMD scores and each frequency they were treated with. That is, responders to one frequency (i.e. 1 or 20 Hz) tended to deteriorate when the other frequency was applied (i.e. 20 or 1 Hz). Overall, however, there was a greater response to 1 Hz rTMS compared to 20 Hz rTMS. Additionally, in 11 patients who received PET scans, change in HAMD scores in response to rTMS was related to baseline glucose metabolism measures. Two weeks of 20 Hz rTMS was correlated with baseline global metabolism, with improved response associated with greater baseline global hypometabolism. Conversely, baseline global hypermetabolism was more closely associated with greater HAMD change scores following 1 Hz rTMS. The results suggest that brain metabolic biomarkers may be an effective way of optimising or personalising rTMS treatment response.

In addition to this initial PET research, studies have used a number of other methods to explore brain activity pre- and posttreatment. Research using functional magnetic resonance imaging (MRI) has indicated that high-frequency left-sided rTMS produces a bilateral prefrontal increase in task-related activation [56].

Interestingly, in the same study, successful response to low-frequency right-sided stimulation was associated with bilateral reductions in prefrontal activity. These bilateral changes suggest that successful response to rTMS treatment is not related to a simple rebalancing of left–right activity and that response to treatment may involve alternative mechanisms. Interestingly in this context, recent studies have suggested that response to rTMS may be related to changes in white matter pathways in prefrontal–subcortical circuitry [57]. This research suggests that rTMS response does not necessarily relate to local changes in cortical activity but arises through strengthening of cortical–subcortical circuitry. Strengthening of these connections could potentially allow executive prefrontal cortical regions to exert greater regulatory control over abnormally active subcortical mood circuitry.

3.4.3 Studying Brain Effects of rTMS with Near-Infrared Spectroscopy

An alternative mechanism of exploring the effects of rTMS stimulation on brain activity is through the use of near-infrared spectroscopy (NIRS). NIRS is a technique for measuring blood oxygenation (HbO) that can be used in combination with rTMS and repeatedly over time. Initial research using NIRS to study the effects of single-pulse TMS demonstrated quite consistently that higher-intensity TMS results in a drop in HbO, both at primary motor cortex (M1) and at prefrontal cortex (PFC) (e.g. [58, 59]). Subthreshold single-pulse TMS results in a more recognisable increase in HbO than would be expected to be seen during normal brain activation. More recent studies have found that the decrease in HbO that results from high-intensity TMS stimulation can also be seen with paired TMS pulses [59] and rTMS [60]. For example, we recently demonstrated that prolonged trains of 1 Hz rTMS at suprathreshold intensities produced a prolonged and sustained reduction in HbO not seen with subthreshold stimulation [61]. This pattern of substantial HbO reduction appears to be an ‘unnatural’ pattern of brain activation, differing from what would be expected for normal brain activation or engagement in a cognitive task [58, 59, 61, 62]. Speculatively, it is possible that the brain’s response to this unnatural pattern of brain activation, such as a change in vasomotor activity, may in some way underlie the therapeutic action of rTMS.

3.5 Studying Brain Effects of rTMS with Electroencephalography

EEG methods have been used relatively extensively to study aspects of rTMS treatment of depression. Initially EEG was used to investigate whether there were safety-related issues with rTMS treatment. More recently, a series of studies have investigated whether EEG markers can be used to predict successful response to rTMS treatment (e.g. [63, 64]). Of most relevance, however, are studies that have

investigated changes in EEG activity associated with successful antidepressant treatment. For example, Spronk et al. evaluated the effects of rTMS applied over the DLFPC on quantitative EEG (QEEG) and the oddball ERP in patients with depression [65]. They reported that QEEG measures did not change with treatment, with the exception of an indirect right frontal increase in delta power. By contrast, rTMS resulted in an increased positivity in ERPs over the left frontal cortex. Specifically, the P2 amplitude was significantly increased in left frontal regions. There was also a treatment-related increase in N1 and N2 ERP components. These results suggest that rTMS can alter conventional neurophysiological markers of plasticity in the cortex. Such measures may ultimately serve as biomarkers of treatment response and help tailor or personalise rTMS treatment.

3.6 Effects of rTMS on BDNF

Given the postulated role of neurotrophic factors, including BDNF, in the aetiology of depression and the mechanism of action of antidepressant medication, studies have increasingly explored whether the antidepressant effects of rTMS are modulated through rTMS-induced changes in BDNF. These studies have occurred both in animal models and in human experimental settings.

For example, high-frequency rTMS was shown to produce a substantial increase in BDNF levels in rats when stimulation was applied in awake animals, an effect not seen with low-frequency stimulation [66]. In a second study, three weeks of high-frequency stimulation was also shown to produce increases in BDNF levels along with changes in hippocampal cell proliferation [67]. In humans, Bocchio-Chiavetto et al. [68] reported that 5 daily sessions of rTMS administered to 16 patients with MDD resulted in significantly improved depression (average improvement by HAMD of 23.60 %; $p = 0.0003$) with a concomitant increase in serum BDNF levels (baseline 29.73 ± 8.02 ng/mL; posttreatment 32.63 ± 7.59 ng/mL; $p = 0.022$). However, the clinical relevance of these findings is uncertain as the authors reported the increment in the neurotrophin levels was not associated with rTMS efficacy. Additional evidence from Lang et al. [69] also failed to detect an association of BDNF with clinical improvement following 10 rTMS treatments of 14 patients suffering from treatment-resistant major depression.

The relationship of the BDNF system to rTMS response has also been explored in human subjects by considering the relationship between clinical response to treatment and BDNF genotype, specifically the effect of the val66met BDNF polymorphism. In a study of 36 patients where 31 had a diagnosis of major depression and the remainder five of bipolar disorder (depressive phase), five daily sessions of rTMS improved patient HAMD scores (baseline 23.19 ± 5.12; post-rTMS 17.50 ± 6.91; average = 25.29 %). The val/val homozygotes (32.36 ± 21.23 % improvement in HAMD) experienced a much greater improvement than met carriers (16.45 ± 19.90), indicating a role for this polymorphism in the improvement of depressive symptoms with rTMS treatment [68].

Conclusions

In summary, this chapter focused on rTMS mechanisms potentially associated with therapeutic improvement in depression. Treatment effects may relate to potentiation of excitatory and inhibitory cortical mechanisms. It is possible that rTMS responses relate to local changes in cortical activity but also that response relates to an alteration of connections between prefrontal and subcortical brain regions relevant to depression. In addition, evidence suggests that rTMS may modulate plasticity in the cortex. Finally, both BDNF and dopaminergic increases have been reported, both of which have been related to the therapeutic mechanisms of rTMS. Future studies aiming to closely associate changes in these brain mechanisms to changes in symptomatic response may help clarify the physiological basis for the therapeutic effects of rTMS and potentially lead to optimised treatments.

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