

# Neurofeedback and Neuromodulation Techniques and Applications

Edited by Robert Coben • James R. Evans



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# **NEUROFEEDBACK AND NEUROMODULATION TECHNIQUES AND APPLICATIONS**

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Edited by

**ROBERT COBEN**

**JAMES R. EVANS**



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# Repetitive Transcranial Magnetic Stimulation in Depression: Protocols, Mechanisms, and New Developments

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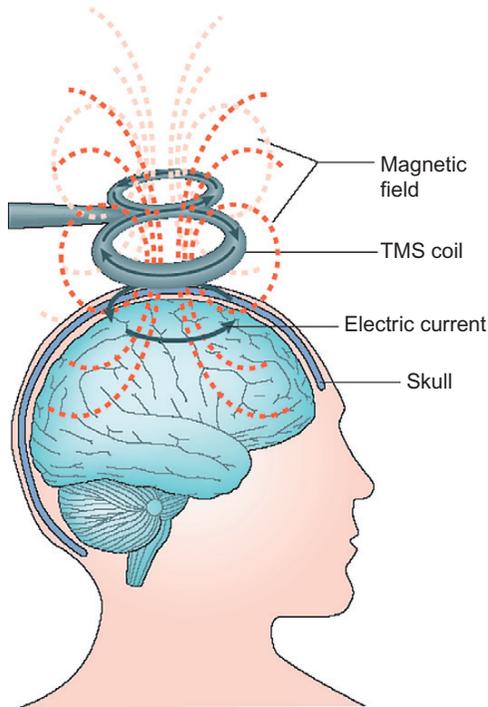
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## INTRODUCTION

TMS (transcranial magnetic stimulation) is a non-invasive neuromodulation technique. Nevertheless, it has a very direct influence on brain physiology. The basic principle of TMS is the application of short magnetic pulses over the scalp of a subject with the aim of inducing electrical currents in the neurons of the cortex. A typical TMS device consists of a stimulator that can



**Figure 10.1** Visual illustration of the induction of electrical currents in the brain through the magnetic pulses (dashed lines) applied by means of the coil (8-shaped figure) positioned above the head. (*Adapted from Ridding and Rothwell, 2007.*)

generate a strong electrical current, and a coil in which the fluctuating electrical current generates magnetic pulses. If the magnetic pulses are delivered in the proximity of a conductive medium, e.g. the brain, a secondary current in the conductive material (e.g., neurons) is induced (Figure 10.1). In the practice of TMS, a subject is seated in a chair and an operator positions the coil above the scalp of the subject, tunes the stimulation parameters of the stimulator, and applies the TMS pulses.

Anthony Barker and his colleagues at the University of Sheffield were the first to develop a TMS device, introducing a new neuromodulatory technique in neuroscience. The first application, demonstrated first by these researchers, was the induction of a motor evoked potential (e.g., activating the muscles abducting the thumb) by means of applying a TMS pulse over the motor cortex (Barker, Jalinous, & Freeston, 1985).

Initially, TMS was used mainly in studies on motor conductivity through investigating the temporal aspects and amplitude of the evoked

motor responses after stimulating the motor cortex. Continuing progress on the technical aspects of TMS devices soon made it possible to deliver *multiple* pulses within a short time period, i.e., repetitive TMS (rTMS). With the development of rTMS, researchers were able to induce changes that outlasted the stimulation period (Pascual-Leone et al., 1999). This has led to a considerable extension of the possible applications of TMS. Currently, rTMS is used for an increasing variety of applications such as the study of pathophysiology of diseases, the investigation of the contribution of certain brain regions to particular cognitive functions and, most relevant for this chapter, the treatment of psychiatric diseases.

The potential of repetitive TMS in the treatment of psychiatric disorders was suggested for the first time relatively soon after the development of the first TMS device in 1985. In a study on motor conductivity, changes in mood in several normal volunteers who received single pulses over the motor cortex were described (Bickford, Guidi, Fortesque, & Swenson, 1987). Following this initial observation, the technical progress and the increasing availability of TMS devices has led to the opportune investigation of rTMS in the treatment of depression. Apart from being the *first* investigated psychiatric application, it is also the *most* investigated psychiatric application in many centers all around the world. In addition, a TMS device has been approved by the FDA in late 2008, and a growing number of private outpatient as well as hospitalized patients with depression are treated in clinical settings (approximately 150 US centers in the middle of 2010).

Major depression is a common disorder, with millions of sufferers around the world and a lifetime prevalence of about 13% in men and 21% in women (Blazer et al., 1994). The World Health Organization has predicted that depression will globally become the second largest burden of disease by 2020, following cardiovascular conditions (Murray & Lopez, 1997). Individuals with depression experience a wide range of symptoms, including a loss of interest or pleasure, feelings of sadness, guilt, low self-esteem, disturbances in sleep and appetite, poor concentration and suicidal ideations (DSM-IV, American Psychiatric Association, 1994). It is obvious that major depression has a disabling effect on daily activity, indicating that effective treatment is crucial. Treatment with antidepressant medication is the most common and first line treatment for many individuals. However, a significant percentage of patients do not sufficiently respond to antidepressant medication (Keller et al., 2000; Kirsch et al., 2008; Rush et al., 2006) and some of the patients proceed to electroconvulsive therapy (ECT). Despite

some remarkable clinical results (Husain et al., 2004), ECT is a controversial and unpopular treatment option due to the required induction of a seizure and associated side-effects such as memory loss (Robertson & Pryor, 2006). Following initial positive results with depression, and due to its painless and non-invasive administration, rTMS has been proposed as a “better” alternative to ECT (Paus & Barrett, 2004) or as an alternative for patients who may not be willing to undergo ECT, or for whom ECT may not be suitable. In order to compare efficacy of these treatments, rTMS and ECT have been jointly investigated in several studies (Eranti et al., 2007; Rosa et al., 2006). Of the several studies performed, Eranti et al., (2007) observed a great advantage for ECT. However, others (Grunhaus et al., 2003; Pridmore et al., 2000; Rosa et al., 2006) found comparable efficacy rates for ECT and rTMS in the treatment of depression. Notably, studies that have reported an advantage of ECT have compared an unlimited number of usually flexibly administered (unilateral or bilateral) ECT treatments to a fixed number of only one type of rTMS, potentially biasing the results of these studies. In addition, Eranti et al. (2007) included patients with psychotic depression whereas the other studies only involved non-psychotic depression (Grunhaus et al., 2003; Pridmore et al., 2000; Rosa et al., 2006), suggesting that rTMS might not be the best treatment option for the treatment of depression with psychotic features.

The early reports of rTMS as an antidepressant treatment modality consisted of pilot studies with a small number of subjects. In these early studies arbitrary stimulation parameters over various and non-specific brain regions were applied (Höflich et al., 1993; Kolbinger et al., 1995). A report by George et al. (1995) showed robust improvements in depressive symptoms in two out of six patients. This study marked the start of the serious pursuit of rTMS as a potential treatment option for depressed patients. Subsequently, a reasonably large number of open-label as well as randomized sham-controlled studies were performed. Most studies found a moderately favorable treatment effect for rTMS using various designs (Avery et al., 2006; Fitzgerald, Huntsman, Gunewardene, Kulkarni, & Daskalakis, 2006; Fitzgerald et al., 2003; George et al., 2010; Mogg et al., 2008; O’Reardon et al., 2007; Padberg et al., 1999; Rossini et al., 2005), which has recently been confirmed by several meta-analyses (Schutter, 2009; Schutter, 2010). However, some researchers could not replicate these findings and found no differences between sham and active treatment conditions (Loo et al., 2003; Nahas, Kozel, Li, Anderson, & George, 2003).

After 15 years of research, the general consensus is that rTMS treatment in depression *has* potential, but has not yet fully lived up to initial expectations. In large part this is due to limited understanding of the mechanisms underlying the clinical treatment effect. A substantial research effort, already in progress, may elucidate the mechanisms of the beneficial effects of rTMS in depressed patients. Hopefully, results of this effort will lead to continued improvements in treatment protocols, and provide patients with the best possible treatment of their depression.

In this chapter, a comprehensive overview of rTMS in the treatment of depression will be provided. In the first section various rTMS protocols will be reviewed in terms of the different stimulation parameters that are of interest. Subsequently, some potential physiological mechanisms that are associated with antidepressant outcome will be reviewed. In regard to this, we present an overview of rTMS-induced effects found in imaging studies, pharmacological studies, and genetic studies. Finally, we will address new developments in the field.

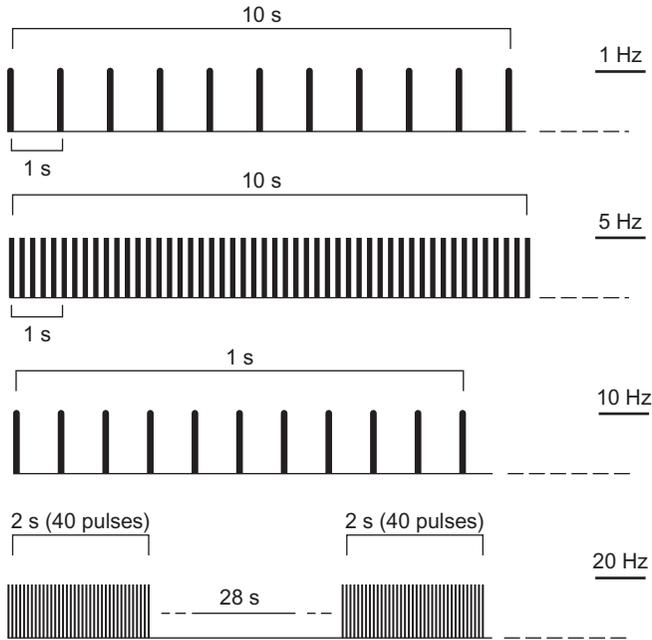
## PROTOCOLS

The behavioral effects of rTMS have been found to depend on the frequency, intensity, and duration of stimulation (e.g. Avery et al., 2006; Fitzgerald et al., 2006b; O'Reardon et al., 2007; Padberg et al., 2002). The most important parameters that rTMS protocols in depression can be distinguished on are the stimulation frequency and the stimulation location. These will be discussed at length by reviewing literature that used diverse choices for these parameters. Some other relevant parameters (intensity, number of trains, inter-train interval, and number of sessions) will be briefly described. In Figure 10.2, some of the characteristics of an rTMS stimulation protocol are illustrated.

Progress in the development of technical aspects of TMS devices and advancing insights have led to a continuing progression of experimental and innovative protocols. Some more recently developed protocols investigated in the treatment of depression, such as theta burst stimulation and deep TMS stimulation, are discussed in the section “New Developments”.

### Stimulation Frequency

The stimulation frequency refers to the number of pulses delivered per second, as can be programmed on the TMS device. Examination of these rTMS studies in depression reveals that, at first glance, two types of studies



**Figure 10.2** Examples of 10 s of rTMS at 1 Hz (first trace) and at 5 Hz (second trace); 1 s of rTMS at 10 Hz and an example of 20 Hz application (trains of 2 s interleaved by a pause of 28 s). (Adapted from Rossi, Hallett, Rossini, Pascual-Leone, & The Safety of TMS Consensus Group, 2009.)

can be discerned: studies performing high-frequency (also referred to as fast) rTMS (HF-rTMS) and studies in which low frequency (also referred to as slow) rTMS (LF-rTMS) parameters are applied. HF-rTMS usually includes frequency parameters of 5 Hz or above, whilst LF-rTMS incorporates stimulation frequencies of 1 Hz or below. HF-rTMS is usually applied over the left prefrontal cortex, whilst LF-rTMS is mostly applied over the right prefrontal cortex (see “Stimulation Location” below for a more elaborate review). In addition to studies applying solely HF-rTMS or LF-rTMS, combined approaches have been proposed.

### **High-Frequency rTMS**

Most rTMS studies in depression to date have been performed by means of applying high-frequency stimulation (Avery et al., 2006; George et al., 2010; O’Reardon et al., 2007). HF-rTMS protocols have mostly used stimulation frequencies of 10 Hz (but this has varied from 5 to 20 Hz).

In the largest study to date, O'Reardon et al. (2007) reported significantly better clinical results in an active rTMS group in comparison to the sham group, as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). This was a randomized study in which 301 medication-free patients were treated with 10 Hz stimulation frequency. In a recent non-industry sponsored trial, George and colleagues (2010) demonstrated that 10 Hz HF-rTMS yielded a remission rate of 14% in the active group as compared to 5% in the sham. The total number of intention-to-treat patients was 190, a group that was characterized by a highly treatment-resistant depression. Apart from these large multi-center studies, numerous single site studies applying stimulation frequencies of 10 Hz have been performed. These have showed response (more than 50% decrease on the depression scale) rates between 30 and 50% (Avery et al., 2006; Garcia-Toro et al., 2001; George et al., 2010; Mogg et al., 2008; O'Reardon et al., 2007; Padberg et al., 1999; Rossini et al., 2005). Most of these studies have been performed in treatment-resistant patients. A few trials that have applied frequencies of 5, 17, or 20 Hz have been reported (Fitzgerald et al., 2006b; Luborzewski et al., 2007). In Fitzgerald's study (Fitzgerald et al., 2006b), patients who did not respond to a protocol with frequencies of 1 or 2 Hz (LF-rTMS see below) were assigned to either 5 Hz or 10 Hz HF-rTMS protocol. No significant differences in response to 5 or 10 Hz were shown. In addition, Luborzewski and colleagues (2007) have shown beneficial treatment effects in patients who had received 10 sessions of 20 Hz rTMS. Due to the limited number of studies no definitive conclusions can be drawn, but results suggest that 5, 17 or 20 Hz stimulation frequencies do at least have antidepressant effects. However, some reports have shown differential effects of different stimulation parameters, including a report of 9 Hz rTMS tending to be less beneficial than 10 Hz (Arns, Spronk, & Fitzgerald, 2010). To summarize, it is not yet known which exact frequencies appear to be the most beneficial in HF-rTMS, but 10 Hz rTMS has been investigated best and is often used.

### ***Low-Frequency rTMS***

In addition to the HF-rTMS studies in the treatment of depression, several LF-rTMS studies have been performed (Fitzgerald et al., 2003; Januel et al., 2006; Klein et al., 1999). For example, Klein et al. (1999) showed in a large sham-controlled study that 1 Hz rTMS, in which 70 patients were randomly assigned to sham or active treatment, yielded a response

rate of 49% in the active treatment as compared to 25% in the sham. This study also showed a significant larger improvement in depression scores in the active as compared to the sham group. In the largest controlled study on LF-rTMS in depression, 130 patients were initially assigned to a stimulation protocol of either 1 or 2 Hz (Fitzgerald et al., 2006b). Of the 130 patients enrolled, approximately 51% could be classified as responders after 10 days of treatment. Interestingly the response rates between the 1 Hz and 2 Hz did not significantly differ. Although LF-rTMS is a more recently developed protocol and is less well studied, it appears to have beneficial effects comparable to HF-rTMS.

In order to systematically investigate if HF or LF-rTMS is more beneficial, protocols were directly compared (Fitzgerald et al., 2003; Fitzgerald, Hoy, Daskalakis, & Kulkarni, 2009; Isenberg et al., 2005). In a double-blind, randomized, sham-controlled study, 60 treatment-resistant patients were allocated into three groups; one received HF-rTMS trains to the left prefrontal cortex at 10 Hz, the second group received LF-rTMS trains at 1 Hz to the right prefrontal cortex and the third group received sham treatment. The clinical results showed that the groups treated with HF-rTMS and LF-rTMS had a similar reduction in depressive symptoms, and for both groups, treatment response was better than within the sham group (Fitzgerald et al., 2003). In another study with a similar aim, 27 subjects were assigned to either HF-rTMS (10Hz) or LF-rTMS (1Hz) rTMS. It was concluded that both treatment modalities appeared to be equally efficacious (Fitzgerald et al., 2009a). Schutter (2010), based on a meta-analysis of all randomized controlled LF-rTMS studies in depression, suggested that LF-rTMS might even be more beneficial than HF-rTMS. However, direct comparisons of the effect sizes of HF and LF-rTMS did not show a statistically significant difference. More research with larger samples is required to confirm these findings and demonstrate if LF-rTMS and HF-rTMS are similarly efficacious, or if LF-rTMS is more efficacious than HF-rTMS. Aside from the comparison of clinical effects, it appears that LF-rTMS is better tolerated, i.e., patients reported less headaches. It may also minimize the risk of inducing adverse events like seizures (Schutter, 2010).

Although the vast majority of studies have focused on low-frequency stimulation applied to the right and high-frequency stimulation applied to the left prefrontal cortex, it is to be noted that in a few studies parameters have varied from these traditional sites. Some have suggested that low frequency stimulation applied to the left may also have antidepressant effects, thus questioning the traditional model of laterality in depression.

### ***Combined HF and LF-rTMS protocols***

These aforementioned studies demonstrate evidence that active HF-rTMS and LF-rTMS are more effective in the treatment of depression as compared to sham. However, HF-rTMS and LF-rTMS are not necessarily incompatible with each other. In recent years, add-on, bilateral-sequential, and priming protocols have been postulated and investigated.

Add-on protocols concern the combination of one protocol with another protocol, e.g., when patients do not respond to LF-rTMS after several sessions, they can proceed to HF-rTMS treatment. In the aforementioned study by Fitzgerald et al. (2006b) in which LF-rTMS was investigated, non-responders to the low frequency protocol subsequently were treated with HF-rTMS. A subset of these LF-rTMS non-responders did respond to HF-rTMS. Hence, it is likely that different protocols act through different mechanisms and that different patient groups are susceptible to different approaches. It could also be argued that subjects in the add-on protocol received more sessions, and possibly needed longer to respond to treatment. Thus, the full extent of the increase in response rate might not solely be attributable to the change in stimulation frequency.

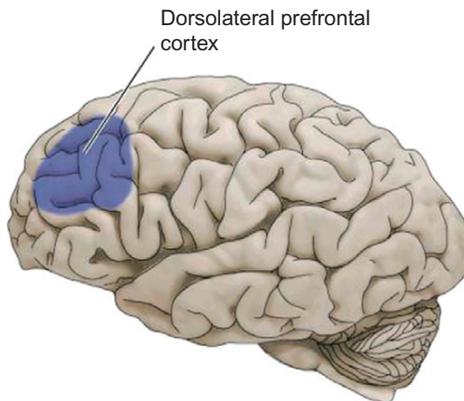
A second variant is the sequential stimulation protocol in which within one session both HF-rTMS and LF-rTMS are applied. This protocol was examined in a double-blind study that included 50 patients with depression. Half of the group received 1 Hz rTMS over the right prefrontal cortex, followed by HF-rTMS over the left prefrontal cortex in the same session, for a period of 4–6 weeks. The other half of the patients received sham stimulation in the same protocol. The higher response rates in the treatment group (44% vs. 8% in sham) suggested that a within-session LF/HF combination protocol might be more effective than applying either protocol alone (Fitzgerald et al., 2006a). However, this hypothesis could not be confirmed by a recent study by Pallanti et al. (2010) in which a sequential combination protocol was compared with unilateral LF-rTMS and sham. Of the three groups, patients who were treated with the unilateral LF-rTMS protocol benefited most from treatment. The authors propose that these results, in contrast to the findings of Fitzgerald et al. (2006a), suggest that a “simple” unilateral protocol is the first treatment of choice. Nevertheless, the authors believe that it remains relevant to further explore combination protocols and compare them to traditional unilateral protocols.

A third option is the unilateral combination of high and low frequency stimulation in a protocol referred to as “priming” stimulation. This involves

the application of low intensity high-frequency trains (usually 6 Hz) followed by standard low frequency stimulation. Basic neurophysiological studies have shown that priming stimulation results in greater suppression of cortical excitability than low-frequency stimulation applied alone (Iyer, Schleper, & Wassermann, 2003). A single clinical study has compared such priming stimulation to 1 Hz TMS (both applied to the right side) and shown a greater clinical effect in the priming group compared to the sham group (Fitzgerald et al., 2008).

### Stimulation Location

The dorsolateral prefrontal cortex (DLPFC) has been the primary area of interest for stimulation (see Figure 10.3). The motivation behind choosing this brain area stems from various imaging studies that indicated depression is associated with regional brain dysfunction in, among other regions, the DLPFC (Cummings, 1993). Other researchers have not only proposed an “underactivated” L-DLPFC, but suggested an imbalance between frontal regions. For example, the “frontal asymmetry hypothesis” of depression states that in depression there is an imbalance in left vs. right frontal brain activation (Henriques & Davidson, 1990; but also see Chapter 4 in this volume). In addition, of all brain regions known to be related to the pathophysiology of depression (e.g., prefrontal, cingulate, parietal, and temporal cortical regions, as well as parts of the striatum, thalamus, and hypothalamus) the DLPFC is regarded as most accessible for treatment with rTMS (Wassermann & Lisanby, 2001). On the basis of such previous theories and



**Figure 10.3** Image of the location of the (left) dorsolateral prefrontal cortex in the brain.

findings, the supposedly activating/HF-rTMS protocols are applied over the left DLPFC and supposedly inhibiting/LF-rTMS protocols are applied over the right DLPFC. The choice of the stimulation frequency is thus closely linked to the stimulation location.

In most studies, localizing the DLPFC has been performed by means of the “5 cm rule”. The hand area of the primary motor cortex (M1) (which elicits a contralateral motor response of the thumb when stimulated), is taken as the detectable reference point. From there, the coil is moved 5 cm anteriorly, in a sagittal direction. Positioning the coil at that location during treatment is assumed to target the DLPFC. It can be argued that this literal “rule of thumb” has some flaws and may result in inconsistent results between sessions within subjects. Moreover, it may not target the DLPFC at all due to differences in head size and shape across individuals and – even more relevant – in the folding patterns of the cortex. In order to solve this problem, technical advances have enabled structural MRI-based neuronavigation systems. In neuronavigation, an MRI of a patient’s brain is acquired before treatment. A series of software co-registrations are made between real anatomical points on the head (which are fixed in location) and the corresponding anatomical points in a three-dimensional reconstruction of the patient’s MRI scan. This allows one to establish the scalp point that corresponds to a location on the brain scan that becomes the proposed target for TMS treatment. A more complicated process can also allow the position and orientation of the coil relative to the corresponding brain region to be monitored in real time. In a study by Herwig et al. (2001) the reliability of the “5 cm rule” was investigated by means of comparing the target area defined by the “5 cm rule” with the target defined by DLPFC neuronavigation. Of the total 22 subjects, the targets corresponded in only seven. In a similar study, it was found that the true DLPFC was in general located more anteriorly to the site traditionally identified by the “5 cm rule” (Fitzgerald et al., 2009b).

Together, these studies suggest that clinical efficacy may be improved by means of more precise targeting methods. This has been directly tested in one study with 52 patients who were randomized to stimulation localized by the “5 cm rule” or neuronavigation (Fitzgerald et al., 2009b). Neuronavigationally targeted treatment resulted in a statistically significant greater response in depression scores than treatment targeted by the traditional method.

Despite the fact that the majority of the studies target the DLPFC, some authors have argued that it has never been experimentally proven

that the DLPFC is the most effective target for rTMS treatment of depression. In addition, the pathophysiology of depression is certainly not limited to the DLPFC (Drevets, Price, & Furey, 2008). Investigation of antidepressant effects of rTMS applied to other brain regions has therefore been explored (Schutter, Laan, van Honk, Vergouwen, & Koerselman, 2009). Schutter and colleagues (2009) applied 2 Hz rTMS at 90% of the motor threshold (see next section) to the right parietal cortex in a group of patients with depression for a period of 10 sessions. Their findings did not show statistically significant changes between the active and sham group. However, comparison of both groups on a partial response outcome (at least a 30% reduction in HAM-D score) showed a significantly higher response in the active rTMS group as compared to the sham group. This result suggests that targeting the right parietal cortex with 2 Hz rTMS may have antidepressant properties, although the effects were not as strong as compared to frontal HF or LF-rTMS. Although these findings need to be replicated in larger studies, they are encouraging regarding searching for other cortical targets in the treatment of depression with rTMS.

### **Stimulation Intensity, Trains, and Sessions**

For rTMS to be effective, the magnetic field has to induce currents in the neurons of the cortex. The intensity of the magnetic field that induces this current is referred to as the stimulation intensity. This is usually expressed as a percentage of the motor threshold (MT). The MT is usually determined prior to each session by applying the TMS coil over the “thumb” area of the motor cortex. Single pulses are applied by stepwise variation of the output intensity of the device. The minimal output intensity which yields a motor response (moving of the thumb) in at least half of the applied trials is determined to be the MT. So if the intensity of a TMS protocol is 100% MT, then it is the same as the output intensity of the device which was determined to be MT. All other intensity values are reflected as a percentage of this MT, e.g., if the MT is at an output intensity of the device of 60%, then an intensity of 110% MT means that the output intensity is 66%. Although this determination of stimulation intensity may seem arbitrary, it takes individual differences in motor cortex excitability (and therefore excitability of other brain regions) into account. This contributes to a safer administration of TMS pulses to an individual. In depression protocols reported to date, the lowest stimulation intensity used was 80% MT (George et al., 1995) and the maximal intensity used

was 120% MT (O'Reardon et al., 2007; Rumi et al., 2005). The majority of the depression protocols use stimulation intensities of 100% MT or 110% MT. In a study by Padberg et al. (2002), in which the relation between treatment efficacy and stimulation intensity was investigated, patients who were treated with a HF-rTMS (10 Hz) protocol at 100% MT showed a 30% decrease in depressive symptoms as measured by the HAM-D, as compared to a 15% decrease for patients who were treated with the same protocol but at 90% MT. This result, among others, suggests more beneficial outcomes for higher stimulation intensities. Therefore, more recent studies have used intensities of 110% and 120% MT (O'Reardon et al., 2007; Rumi et al., 2005), in contrast to earlier research where intensities between 80% and 100% MT were more common (George et al., 1997; Kimbrell et al., 1999).

In most rTMS protocols the stimulation is delivered in pulse trains (see Figure 10.2). That is, pulses are delivered in series separated by certain time intervals – the inter-train interval (ITI). This is done for two reasons. First, the effect of TMS pulses is cumulative in the brain (Hallett, 2007; Ridding & Rothwell, 2007), and this summation causes an increase of the likelihood of the induction of a seizure (the most serious potential side effect associated with rTMS). In several reports, safety guidelines in which maximum recommended values of stimulus parameters like stimulus intensity, train duration, number of trains, and ITI are provided for the safety of the patients (Rossi et al., 2009; Wassermann, 1998). Secondly, the repetitive release of strong electrical pulses causes heating of the electronics of the TMS device. The ITI between trains allows the device to partially cool down. Due to safety reasons for the subject and protection of the device, all devices are manufactured to automatically turn off as soon as a certain heat-limit has been reached. Newer TMS devices are designed with better cooling systems (e.g., air- or fluid-cooled coils), which reduce the likelihood of overheating. However, the overheating of the device is still possible when multiple sessions are performed within a short period, or if a highly demanding (e.g., high rate of pulse delivery) protocol is performed. Train durations in HF-rTMS protocols are usually between 2 and 10 seconds with an ITI between 20 and 60 seconds. In LF-rTMS protocols often continuous stimulation is used.

In studies performed thus far, the number of sessions applied has been highly variable, ranging from five sessions (Manes et al., 2001; Miniussi et al., 2005) to up to or greater than 30 sessions (Fitzgerald et al., 2006b; O'Reardon et al., 2007). However, to date, the majority of studies have

involved a total of 10 sessions (for example, Fitzgerald et al., 2003; Garcia-Toro et al., 2001; Koerselman et al., 2004; Poulet et al., 2004). Based on more recent studies, a general trend towards a greater number of sessions (>10) is associated with continuing improvement in depression scores (Fitzgerald et al., 2006b; Rumi et al., 2005). Schutter (2009) suggested that similar to antidepressant medication, rTMS treatment may involve a delayed therapeutic onset. Investigation of the number of sessions optimally required is important for gaining information about the temporal course of the antidepressant effect.

The variety of protocols discussed above indicate that rTMS is an active field of research. Treatment outcome has been shown to vary with protocols, but some protocols have proven their efficacy. However, it has been argued that it is unlikely that the current combinations of stimulation parameters potentiate optimum clinical effects. It is likely that there is much room for improvement, and studies directly addressing the question of optimal stimulation parameters are urgently required. This statement is further supported by the finding that early rTMS depression protocols have shown less favorable results compared to relatively newer, more promising protocols (Gross et al., 2007). Increasing knowledge about the mechanisms underlying treatment efficacy – the topic of the next section – may result in new protocols with closer to optimal treatment effects.

## **MECHANISMS OF rTMS TREATMENT IN DEPRESSION**

With rTMS the goal is to modulate brain activity, with a resultant reduction of depressive symptoms. Although clinical results appear promising, mechanisms explaining the symptomatic reduction are unknown. In order to optimize rTMS for therapeutic use, it is necessary to gain a better understanding of possible neurobiological mechanisms underlying the clinical response. This is currently a topic of active interdisciplinary research.

Knowledge of neurobiological mechanisms to date is derived from neuroimaging studies, studies on neurotransmitter and neuroendocrinologic systems, and from gene expression research. Together, these efforts will hopefully explain the substrate of the antidepressant effects of rTMS. In the following paragraphs, studies in each of the fields mentioned above on rTMS-induced changes will be reviewed. The neurophysiology of rTMS at the neuronal level in general is outside the scope of this review. However, the interested reader is referred to an excellent review by Wassermann and colleagues on this topic (Wassermann et al., 2008).

## Neuroimaging

The combination of rTMS with neuroimaging research provides a unique opportunity to elucidate the underlying mechanisms of rTMS in the treatment of depression. Most imaging studies to date have used positron emission tomography (PET) or single-proton emission computed tomography (SPECT) to identify brain regions with altered blood flow or glucose metabolism as a result of rTMS. These modalities have lower temporal resolution compared to functional magnetic resonance imaging (fMRI), and therefore not much is known about the time course of brain activation in response to rTMS. Recently, however, some studies using near-infrared spectroscopy (NIRS) have been performed (Aoyama et al., 2009; Hanaoka, 2007; Kozel et al., 2009).

As discussed in the “Protocols” section, in most depression protocols rTMS is applied over the left or right DLPFC. Several neuroimaging studies have indeed demonstrated rTMS-induced changes within the DLPFC. HF-rTMS over the left DLPFC of depressed patients induces a local increase in regional cerebral blood flow (rCBF) as indicated by SPECT (Catafau et al., 2001; Loo et al., 2003; Kito et al., 2008a; Speer et al., 2000) and fMRI BOLD response (Cardoso et al., 2008). In contrast, imaging studies of LF-rTMS over the right DLPFC showed a local *decrease* in rCBF (Kito, Fujita, & Koga, 2008; Loo et al., 2003; Speer et al., 2000). It should be noted, however, that in an fMRI study Fitzgerald and colleagues (2007) could not replicate the local decrease in BOLD response following LF-rTMS. Instead, a bilateral frontal reduction in BOLD response was observed.

In early studies using PET/SPECT it was shown that changes in brain activation induced by rTMS were not limited to the stimulated area (Paus, Jech, Thompson, Comeau, Peters, & Evans, 1997). A single TMS pulse can lead to effects in more distal brain areas within the same network as the stimulated area (Siebner et al., 2009). In a similar vein, rTMS-induced changes in brain activity in depression may not necessarily be limited to the DLPFC; remote regions are often in good accordance with areas known to be associated with the pathophysiology of depression (reviewed in Fitzgerald et al., 2006c). In support of this theory, imaging studies cited above have also found changes in blood flow in remote/subcortical brain regions following rTMS (Baeken et al., 2009; Loo et al., 2003; Speer et al., 2000). Other brain regions that have been reported to show a change in rCBF after HF-rTMS over the left DLPFC are the

ventrolateral prefrontal cortex, right-dominant orbitofrontal cortex, the anterior cingulate, the left subgenual cingulate, the anterior insula, and the right putamen/pallidum (Kito et al., 2008a). Of clinical relevance, it was demonstrated that increases in rCBF in the L-DLPFC are related to significant improvement in clinical outcomes, and that increases in the R-DLPFC and subcortical regions mentioned above are negatively correlated with the change in depressive symptoms (Kito et al., 2008b).

One neuroimaging study has directly compared the effects of high frequency stimulation applied to the left side with low frequency stimulation applied to the right (Fitzgerald et al., 2007). This study, using fMRI recordings during a cognitive task, found that low frequency stimulation produced a bilateral reduction in neural activity whereas high frequency stimulation had the opposite effect. The direction of these effects was in keeping with traditional models of the effect of low and high frequency TMS. However, the fact that changes were produced bilaterally when both groups improved clinically to a similar degree, is not consistent with laterality models of depression, such as that proposed by Henriques and Davison (1990).

Event-related potentials (ERPs), and especially late ERPs, are related to cognitive processes such as attention, stimulus evaluation, and early visual detection. Similar to other psychiatric disorders, a reduced P300 amplitude is often observed in depression (Blackwood, Whalley, Christie, Blackburn, St Clair, & McInnes, 1987; Himani, Tandon, & Bhatia, 1999). In a study by Möller et al. (Möller, Hjaltason, Ivarsson, Stefánsson, 2006) it was demonstrated that active TMS was associated with a significant increase in the P300 amplitude after 5 daily HF-rTMS sessions over the left DLPFC. In a study by our own group it was shown that using an auditory oddball paradigm, patients who were treated with HF-rTMS over left DLPFC showed localized changes on N1, P2, N2, and P300 amplitudes over left frontal areas, but not over the right frontal region. These results were interpreted as an increased positivity in the ERP which was localized to the stimulated area only (Spronk et al., 2008).

These findings demonstrate specific and selective alterations induced by repeated rTMS, which are distinct from those induced by other antidepressant treatments. The rTMS induced effects on neuroanatomical functions are commensurate with some known abnormalities in depression, e.g., decreased rCBF and metabolism values shown in a number of imaging studies (Baxter et al., 1989; Biver et al., 1994). Additionally, other research has shown similar changes in rCBF and metabolism relating to improvement of depression either after spontaneous recovery (Bench,

Frackowiak, & Dolan, 1995) or after treatment with antidepressant medication (Kennedy et al., 2001).

### **Neurochemical Effects: Neurotransmitters and Neuroendocrinology**

Apart from altering rCBF in stimulated regions and connected networks, rTMS also has an effect on the neuroendocrinologic (Post & Keck, 2001) and neurotransmitter systems (Ben-Shachar, Belmaker, Grisaru & Klein, 1997; Strafella, Paus, Barrett & Dagher, 2001). Many lines of research on antidepressant mechanisms have focused on monoaminergic neurotransmission, i.e., through dopamine, norepinephrine and serotonin. Depression is thought to be associated with deficiencies in monoaminergic neurotransmission, and antidepressant medication is thought to act through enhancement of monoamines. These three neurotransmitter systems have also been investigated in relation to rTMS treatment (Ben-Shachar et al., 1997; Keck et al., 2000), and most studies support a role for the dopaminergic system. By means of microdialysis techniques in animal models, it was demonstrated that HF-rTMS induced an increase in the release of dopamine in the hippocampus (Ben-Shachar et al., 1997; Keck et al., 2000; Keck et al., 2002), the nucleus accumbens (Keck et al., 2002; Zangen & Hyodo, 2002) and dorsal striatum (Keck et al., 2002). It should be noted, however, that there are many methodological issues making interpretations from animal rTMS research difficult, such as the size of the head in relation to the coil size.

A few years later rTMS-induced changes in dopamine were investigated for the first time in human subjects. Strafella et al. (2001) found an increased dopamine release after HF-rTMS over the left DLPFC in the ipsilateral nucleus accumbens of healthy subjects by use of PET imaging (Strafella et al., 2001). The observation that increased dopamine levels were found only in the ipsilateral striatal area (site of stimulation) was particularly interesting, because it suggests that the increased release was exerted through cortico-striatal projections from the targeted DLPFC (Strafella et al., 2001). Taking this one step further, Pogarell and colleagues also found an increased striatal dopamine release in a small group of *depressive patients* after HF-rTMS over the left DLPFC by using SPECT (Pogarell et al., 2006; Pogarell et al., 2007). In these two studies, no correlation between the binding factors reflecting dopamine release and clinical outcome could be demonstrated. This needs to be investigated further in larger controlled studies (Pogarell et al., 2006).

In the study performed by Keck and colleagues (2002), a rTMS-induced effect on dopamine was found by using intracerebral microdialysis, but no effects on norepinephrine and serotonin were found. This finding suggests that rTMS mainly targets the dopamine system. Nevertheless, there are some indications that rTMS might modulate serotonergic neurotransmission. For instance, Juckel et al. (1999) showed that *electrical* stimulation of the prefrontal cortex of the rat resulted in an increased serotonin level in the amygdala and hippocampus; a similar pattern of release may occur after stimulation by rTMS. In addition, studies on serotonergic receptors and binding sites (which indirectly provide a measure of availability of certain neurotransmitters in the brain) after a single TMS session in a rat model showed an increase in serotonergic binding sites (Kole et al., 1999), and downregulation of receptors in cortical as well as subcortical areas (Ben-Shachar et al., 1999; Gur, Lerer, Dremencov, & Newman, 2000). With the exception of Keck et al. (2000) who found no effects on serotonin, no rTMS research has been conducted on the serotonergic system in depression models, or in human depressed patients. This makes claims about TMS-induced changes on serotonin release highly speculative. Similarly speculative are claims regarding the effects of rTMS on the third member of the monoaminergic group, noradrenalin (norepinephrine). Limited studies are available and the findings are heterogeneous. Keck et al. (2000) found no changes on noradrenalin. Conversely, a study in mice found increased levels of monoaminergic transporter mRNA after a 20-day rTMS course. That was also associated with the binding and uptake of noradrenalin (Ikeda, Kurosawa, Uchikawa, Kitayama, & Nukina, 2005).

Another possible mechanism through which rTMS exerts its antidepressant effect involves the modulation of GABA and glutamate, which, respectively, are the main inhibitory and excitatory neurotransmitters. Both neurotransmitters are known to be associated with the pathology of depression and change with clinical improvement in depression (Petty et al., 1992). So far, only a few studies have directly addressed rTMS-induced changes in GABAergic neurotransmission. In an animal model, GABAergic levels were increased in hippocampal regions and striatum, and reduced in hypothalamic regions after 15 days of LF-rTMS stimulation (Yue, Xiao-Lin, & Tao, 2009). The same authors looked at glutamatergic changes and found similar results: an increase in glutamate in striatal and hippocampal regions, but a decrease in the hypothalamus (Yue et al., 2009). Additionally, in an *in vivo* study of depressed patients with a specific focus on the nucleus accumbens, changes

in glutamate levels were observed after successful treatment of 10 HF-rTMS sessions (Luborzewski et al., 2007). Interestingly, the pre-treatment baseline level was related to treatment effects. Responders showed lower pre-treatment glutamate levels, and showed the highest increase in glutamate after successful treatment (see also later section on “Optimizing Treatment”). This suggests that in at least some of the patients, a reduction of depressive symptoms may happen through a restoration of relative glutamate levels (Luborzewski et al., 2007).

Repetitive TMS is known to exert changes in excitability thresholds on a neuronal level. It is known that LF-rTMS in particular induces prolonged *decreases* in motor cortex excitability (Chen et al., 1997), while HF-rTMS induces an *increase* in motor cortex excitability (Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994). Cortical excitability is thought to be maintained by a balance of neurotransmitter levels of GABA and glutamate. It can be hypothesized that glutamate and GABA in this animal model is mediated by excitability levels. To the best of the author’s knowledge, only Luborzewski’s study (2007) investigated rTMS-induced changes in levels of glutamate in depressed patients. More research on the release of GABA and glutamate by means of using *in vivo* techniques is needed to better specify the involvement of these neurotransmitters. In addition, future studies should specifically address the relationships between GABA/glutamate, treatment, and outcome.

## Neurotrophins

Another candidate as a mechanism for the rTMS treatment effect in depression is the modulation and release of neurotrophins. BDNF is a neurotrophin, which plays a role in survival of neuronal cells and in synaptic plasticity and connectivity (Bath & Lee, 2006). In patients with depression, abnormal expression of BDNF has been observed (Shimizu et al., 2003) and, moreover, an upregulation as a result of antidepressant medication (Angelucci, Brenè, & Mathé, 2005; Shimizu et al., 2003) has been demonstrated. Since there is extensive literature that indicates a relation between BDNF and depression (and related outcomes), BDNF became another likely candidate to investigate in relation to the antidepressant treatment response to rTMS.

BDNF serum and plasma levels have, in fact, been investigated in several rTMS studies (Angelucci et al., 2004; Yukimasa et al., 2006; Zanardini et al., 2006). In a preliminary study by Lang et al. (2006) no changes in

BDNF serum level were observed after 10 sessions of HF-rTMS treatment. However, other studies on HF-rTMS-induced effects in treatment of depression yielded different findings (Yukimasa et al., 2006; Zanardini et al., 2006). In one study, BDNF serum levels were assessed before and after a series of five rTMS sessions and considered in relation to treatment outcome as rated by the HAM-D. Half of the participants ( $N = 8$ ) were treated with a LF-rTMS design, while the other half ( $N = 8$ ) were treated with a HF-rTMS design. Results showed that BDNF serum levels significantly increased over the treatment period. Interestingly, no changes between the HF and LF group were found, i.e. both showed equal increases in BDNF levels (Zanardini et al., 2006). In a study by Yukimasa et al. (2006) a similar relationship between treatment response and BDNF plasma levels was observed in a group of 26 patients who were treated with HF-rTMS. BDNF plasma levels increased at the end of the treatment period, but solely in patients who could be classified as responders ( $>50\%$  decrease in depressive symptoms as measured on the HAM-D scale) or partial responders ( $>25\%$  decrease in depressive symptoms). Together, these findings suggest that rTMS is indeed able to induce effects on BDNF levels. The finding that BDNF levels were changed only in the responder group suggests that the BDNF level is related to the *clinical* outcome, rather than simply a physiological effect. This is further supported by the finding that responses to HF and LF-rTMS appear to be similar.

## Genetics

In the above-mentioned studies, several likely candidates associated with (and perhaps responsible for) an rTMS-induced antidepressant response were discussed. Another group of candidates includes genetic effects. As discussed in the “Neurotrophin” section, the modulation of the expression of brain-derived neurotrophic factors (BDNF) is a likely modulating factor through which treatment response is exerted. Hence, it is not surprising, that some of the *genetic* studies have focused on BDNF mRNA expression (Müller, Toschi, Kresse, Post, & Keck, 2000). Müller and colleagues investigated BDNF mRNA expression in an animal model involving applying 55 HF-rTMS sessions over a period of 11 weeks. They found significant increases in BDNF mRNA expression in the hippocampus (CA3 region) and parietal and piriform cortices. In addition, in an animal model of vascular dementia, mRNA expression in the hippocampal CA1 area was investigated in two groups of rats; one group received LF-rTMS and the

other group received HF-rTMS for a period of six weeks. Both groups showed an increase in mRNA protein expressions of BDNF (Wang et al., 2010). However, in yet another genetics study, no rTMS induced effects on BDNF mRNA expression could be demonstrated (Hausmann, Weis, Marksteiner, Hinterhuber, & Humpel, 2000), possibly due to a relatively small number of sessions. Further limitations are that effects were not shown in a specific animal model of depression in any of these three studies. Also, the number of studies in this area is limited. For a discussion on genetic polymorphisms and treatment outcome in human patients see the section on “Optimizing Treatment”.

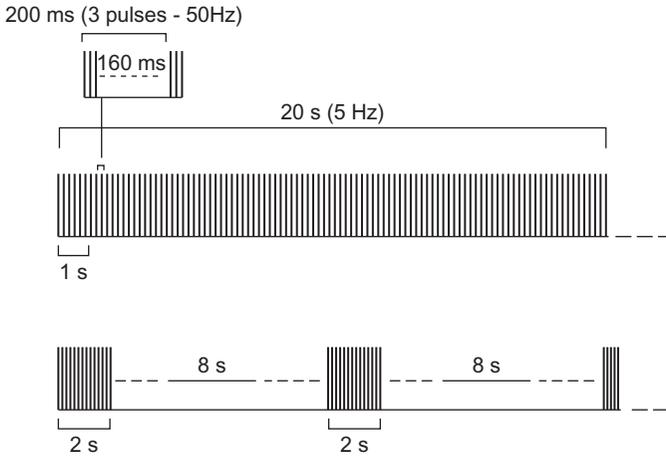
## NEW DEVELOPMENTS

As a new and dynamic field, rTMS is the topic of a considerable research and innovative developments are numerous. These developments are of a diverse nature, including technological progress in equipment and software, protocol innovations and optimizations, and advances in the understanding of long-term effects. Some examples are the investigation of applicability of theta burst stimulation (the delivery of bursts of 50 Hz pulses usually at a rate of 5 Hz) and new equipment such as the H-coil for deeper brain stimulation.

### Progress in Protocols

In addition to the “traditional” LF and HF frequency studies, a newly developed theta-burst stimulation (TBS) protocol has been proposed; referred to as “patterned TMS”. This has been put forward as a technique that could have important implications for the treatment of conditions such as epilepsy, depression, and Parkinson’s disease (Paulus, 2005). TBS usually involves short bursts of 50 Hz rTMS applied at a rate of 5 Hz (hence the name *theta* burst stimulation). In fact there are two frequencies within one train of stimuli; the inter-burst frequency of 50 Hz (e.g., 3 pulses at a rate of 50 Hz) and the frequency of delivery of the number of bursts within one second which is at a rate of 5 per second (5 Hz). TBS can be applied as either a continuous (cTBS), or intermittent (iTBS) train (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). See Figure 10.4 for an illustration of both types of TBS protocols.

Until recently, this rapid delivery of pulses as happens in a TBS protocol was not possible due to technical limitations of older stimulators. TBS has therefore only been investigated since 2005 (Huang et al., 2005).



**Figure 10.4** Examples of the two most common TBS protocols: continuous TBS (first trace) and intermittent TBS (second trace). (Adapted from Rossi et al., 2009.)

In the years after its introduction, it has been shown that TBS induces changes in cortical excitability that may last longer than traditional TMS protocols (Huang et al., 2009; Ishikawa et al., 2007). In regard to the observation of the more sustained effect, Chistyakov, Rubicsek, Kaplan, Zaaroor, & Klein (2010) suggested that TBS might be more effective than traditional HF and LF-rTMS in the treatment of depression. They assigned 33 patients to different types of TBS-TMS treatment protocols over either left or right DLPFC. Despite the relatively high response rate, these findings should be regarded as preliminary and non-specific since no changes between different types of protocols were observed. To the authors' knowledge, this is the only study that has investigated the antidepressant effect of TBS-TMS in the treatment of depression. However, since the TBS protocols are assumed to be more capable of inducing long-lasting effects, it is likely that their application in rTMS depression treatment will increase in coming years.

## Technical Progress

In response to limitations of currently used coils, a new type of coil “the H-coil” (Brainsway) was developed. The coils that are in current use (figure of eight/circular coils) are thought to penetrate underlying brain tissue only to a depth of 1.5–2 cm and are not capable of directly

targeting deeper brain regions (Zangen et al., 2005). H-coils, on the other hand, are capable of stimulating deeper brain regions (Zangen et al., 2005). To date, there are several reports in which it has been presented that brain stimulation by means of the H-coil is safe and that there is potential for use of the coil in clinical applications (Levkovitz et al., 2007; Zangen et al., 2005). The application of the H-coil in the treatment of depression is currently under investigation in a multi-site trial.

## Optimizing Treatment

A better understanding of the neurophysiological and clinical features of depressed patients who respond to rTMS, together with clarity on the neurobiological mechanisms of the induced effect of rTMS treatment in depression, will contribute to the development of more effective forms of rTMS. The field involved in identifying such features is referred to as Personalized Medicine: a research towards establishing patient's characteristics (clinical, physiological or parametric variables) related to (better) clinical outcome. Especially relevant to the rTMS area is the research on identifying objective markers of clinical response. Several studies have focused on addressing this question by investigating specific clinical features. Negative predictors for treatment outcome identified so far are age (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann, & Bajbouj, 2007; Fregni et al., 2006) and therapy resistance (Brakemeier et al., 2007; Brakemeier et al., 2008; Fregni et al., 2006). These results suggest that elderly patients and patients with a greater number of prior treatment failures are less likely to benefit from rTMS. However, this has not been confirmed by all studies in this area (Fitzgerald et al., 2006b). In contrast, a shorter duration of the depressive episode and a high severity of sleep disturbance are predictive of better treatment outcome (Brakemeier et al., 2007).

A different group of potential predictors can be obtained from the neurophysiological data. One study indicated that some patients with depression responded better to LF-rTMS, while others improved only after treatment with HF-rTMS (Kimbrell et al., 1999). These two patient groups differed on pre-treatment baseline regional cerebral blood flow. Patients with a relatively low level of rCBF generally responded better to HF-rTMS (20 Hz), whereas patients displaying relatively high baseline rCBF levels showed a better response to LF-rTMS (Kimbrell et al., 1999). Baeken et al. (2009) showed that higher *bilateral* baseline metabolic activity in the DLPFC and anterior cingulate cortex correlated with better treatment outcome.

In addition, Speer et al. (2009) correlated treatment outcome after 2 weeks of LF or HF-rTMS with pre-treatment baseline perfusion measures. Baseline hypo-perfusion was associated with a more beneficial effect of HF-rTMS compared to LF-rTMS (Speer et al., 2009).

While EEG measures have been relatively well studied in the prediction of treatment response to antidepressant medication (Bruder et al., 2008; Cook et al., 1999; Spronk et al., 2010), their potential in predicting response to rTMS treatment is generally considered limited but promising. In the search for physiological markers for treatment response to rTMS, Price and colleagues (Price, Lee, Garvey, & Gibson, 2008) investigated alpha EEG activity measures, i.e., individual alpha power and frequency, and asymmetry index in 39 patients with treatment resistant depression. None of the measures was found to be a promising candidate for response prediction. Recently Daskalakis, Fitzgerald, Greenwald, and Devlin (2008) were the first to report the potential predictive value of an EEG biomarker initially developed for prediction of treatment response to antidepressant medication. This biomarker (labeled antidepressant treatment response (ATR) index) is measured from frontal electrode positions and is based on the proportion of relative and absolute theta power. In Daskalakis' study it was shown that subjects who could be classified as "responders" after 6 weeks of treatment scored higher on this ATR index. As these early reports indicate, current knowledge of the utility of EEG in the prediction of antidepressant treatment outcome is limited. It has, however, been proposed as having great potential for predicting response to rTMS in the treatment of depression. For example, it has been suggested that rTMS can potentially interact with specific EEG frequency patterns (Funk & George, 2008). In accordance with this notion, Jin, O'Halloran, Plon, Sandman, and Potkin (2006) compared different rTMS stimulation frequencies in the treatment of patients suffering from schizophrenia; two groups received treatment with conventional frequencies, but one group was treated with a stimulation frequency identical to their individualized frontal alpha peak frequency. The group who received the individualized frequency showed a higher reduction in negative symptoms in comparison to the patients who were treated with standard stimulation frequencies. In a report by Arns et al. (2010) a similar approach was taken in the treatment of depression. However, in this study subjects were treated with a stimulation frequency of one Hz above their individualized alpha peak frequency. The results demonstrated this type of individualized stimulation frequency was not

beneficial. In contrast, this study suggested that there could be differential effects of different TMS stimulation frequencies; more specifically, 9 Hz yielded different effects compared to 10 Hz TMS. Furthermore, the study by Arns et al. (2010) demonstrated a clear relation of an individual alpha peak frequency to clinical outcome, where a low alpha peak frequency (7–8 Hz) was associated with lower clinical efficacy. This was also shown in a study by Conca and colleagues (2000) who found that non-responders to rTMS had a slower alpha peak frequency. Clearly, more studies are needed to further explore this.

In addition to demographical and physiological markers, genetic markers may have potential in the prediction of treatment outcome. Several genetic polymorphisms have been investigated in relation to antidepressant treatment outcome in medication studies, for example, BDNF, COMT, and serotonin-related candidate genes (Benedetti, Colombo, Pirovano, Marino & Smeraldi, 2009; Peters et al., 2009; Zou, Ye, Feng, Su, Pan, & Liao, 2010). However, genetics as potential biomarkers for susceptibility to antidepressant medications is still a relatively novel concept, and only a limited amount of research has been conducted. This holds also for the investigation of genetic predictors of rTMS treatment outcome. As discussed previously in this chapter, several studies show treatment-induced changes on BDNF. To date, in respect to the rTMS treatment of depression several genetic polymorphisms have been proposed to be related to treatment outcome. Among them are the genetic polymorphisms associated with BDNF expression, the BDNF Val66Met (Bocchio-Chiavetto et al., 2008; Cheeran et al., 2008) and candidate genes related to expression of serotonin (Bocchio-Chiavetto et al., 2008; Zanardi et al., 2007) (for a discussion of BDNF and serotonin release, see “Mechanisms” above).

Bocchio-Chiavetto and colleagues (2008) demonstrated in their study that carriers of the LL variant of the 5-HTTLPR gene showed significantly greater decreases in depressive symptoms following rTMS (as reflected by percentage decrease on the HAM-D), in comparison to carriers of the S allele. The serotonin-related polymorphisms SERTPR and 5-HT(1A) have also been investigated in relation to depression treatment outcome (Zanardi et al., 2007). Results indicated that polymorphisms related to both genes were to some extent related to treatment outcome, but carriers of the 5HT(1A) C/C gene specifically received more benefit from active rTMS than sham rTMS. This was in contrast to polymorphism carriers of the SERTPR gene, who showed response to treatment outcome regardless of the treatment condition (active or sham).

In addition to their finding on the relation of the 5-HTTLPR with treatment outcome, Bocchio-Chiabetto and colleagues (2008) demonstrated in the same study that BDNF Val/Val homozygotes were better responders than carriers of the Met allele (carriers of MET/MET or MET/VAL). These outcomes can be linked to the study results of Cheeran et al. (2008), who compared differences in excitability measures between Val/Val carriers and carriers of the Met allele. Subjects were investigated using two TBS protocols; a cTBS protocol which is thought to suppress excitability and an iTBS protocol which is known to generally cause an increase in excitability. Change in amplitude measures of the motor evoked potential was taken as an outcome measure reflecting excitability. The results showed that Met allele carriers had less (or no) rTMS-induced changes in excitability; in both TBS protocols no changes in excitability in either direction were evident. Highly speculatively, it can be argued that these results potentially indicate that this same group of Met carriers are less receptive to rTMS-induced clinical improvement. However, it must be emphasized that iTBS and cTBS TMS protocols are very different from traditional HF and LF rTMS depression protocols.

In summary, although rTMS is a relative newcomer among the treatment options for depression, the investigation of “individual characteristics” related to treatment response appears to be progressing rather rapidly. Developments to date seem to mainly focus on fMRI and PET imaging studies and to a lesser extent on genetic polymorphism and EEG parameters. Possibly this is due to the observed direct and indirect interactions with underlying brain regions, and the fact that PET and fMRI imaging are especially effective for highlighting induced changes in regional blood flow and metabolism. The utility of genetic polymorphism in relation to predicting treatment response, in particular the BDNF gene, has potential. TMS devices now allow for a fairly extended choice in treatment parameters (e.g., stimulation intensity, location, frequency etc.). The application of physiological predictors may better guide the parameters to be selected in the future. Evidence for considerable clinical efficacy is required if rTMS is to become accepted as a regular treatment option for depression.

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