

Review

Repetitive transcranial magnetic stimulation of the prefrontal cortex in depression

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ABSTRACT

Transcranial magnetic stimulation is an interesting technique for non-invasively stimulating the brain in awake alert humans. It is a powerful research tool for examining brain behavior relationships. Additionally many researchers are investigating whether repeatedly applying TMS to specific regions over several days to weeks might have therapeutic effects. By far the largest amount of work has been done investigating whether daily applications of prefrontal TMS can improve the symptoms of major depression. We review the literature combining TMS with brain imaging, and then overview the clinical work done to date with TMS in depression. The literature to date suggests that daily prefrontal TMS for several weeks clearly has antidepressant effects, but much work remains to establish the effect sizes and improve the methods of delivery in order to improve its potential clinical utility.

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Introduction

Major depression is among the most common psychiatric disorders and afflicts worldwide 10% of all patients seeking treatment at primary health care facilities (Lopez and Murray, 1998). In particular, therapy-resistant or chronic depression leads to disability with major

economic costs (Hirschfeld et al., 2000). While the therapeutic armamentarium developed over the past few decades has transformed the treatment of major depressive disorder, treatment-resistant depression remains a fundamental clinical problem, with up to 20% of patients not even partially responding and low percentages remitting with antidepressant treatment (Keller et al., 1992; Rush and Thase, 1997). Therefore, treating therapy-resistant depression and preventing chronic depressive conditions constitute major clinical issues. These have generated tremendous interest not only in novel principles of pharmacological treatment, but also in

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novel non-pharmacological approaches such as repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS) and other novel non-pharmacological approaches including novel developments in the important field of psychotherapy.

Repetitive transcranial magnetic stimulation (rTMS) of the dorso-lateral prefrontal cortex (DLPFC) has been introduced to psychiatry for more than a decade and has been largely investigated in terms of its antidepressant efficacy. Unlike electrical stimulation of the scalp, the magnetic pulses of rTMS enter the brain unimpeded and cause neuronal depolarization in a localized area under the coil. Because of the interconnected nature of cortical neurons, rTMS also exerts distant effects localized in networks connected to the site of stimulation (Lisanby and Belmaker, 2000). Generally, two different rTMS modalities have been applied in previous intervention studies: low frequency (LF) rTMS with stimulation frequencies of 1 Hz and high frequency (HF) rTMS with a frequency between 5 and 20 Hz. LF and HF rTMS are proposed to exert opposite effects on cortical excitability (Fitzgerald et al., 2006). Thus, it is hypothesized that rTMS can modulate regional cortical activity in the direction intended to compensate temporary changes of regional brain activity in affective disorders revealed by functional neuroimaging studies. This review summarizes the enormous body of previous research in this field leading from basic research on mechanisms of action to differential clinical applications.

Prefrontal rTMS: mechanisms of antidepressant action

Animal models

Various models of stress and learned helplessness in rodents, which serve as behavioral models of depression, have been explored in order to investigate the antidepressant potential of rTMS. According to several research groups, it was shown that daily rTMS reduces immobility in the forced swim test (Fleischmann et al., 1995; Zyss et al., 1997; Keck et al., 2000a; Sachdev et al., 2002). Similarly, the increase in active coping strategies of animals in this test after pharmacological treatment has frequently predicted the antidepressant efficacy of the investigated drug (Borsini and Meli, 1988). Furthermore, rTMS has also been reported to increase apomorphine-induced stereotypy (Fleischmann et al., 1995). Both findings suggest that in behavioral animal models rTMS may produce antidepressant effects similar to ECT (Belmaker and Grisaru, 1998).

Animal studies have also demonstrated the effects of rTMS on dopaminergic neurotransmission. Using an *in vivo* microdialysis approach, dopamine release following rTMS treatment has been observed in the rat hippocampus, in the striatum, and in the nucleus accumbens septi (Keck et al. 2000b; Keck et al. 2002; Zangen and Hyodo, 2002). The dopamine increase was found after high frequency (20 Hz) rTMS (Keck et al., 2000b; Keck et al., 2002) as well as after low frequency (2 Hz) stimulation (Zangen and Hyodo, 2002). The dopamine increase within the nucleus accumbens was accompanied by an increase of extracellular glutamate in this region (Zangen and Hyodo, 2002). The effects on dopamine could be theoretically mediated both directly, via glutamatergic corticostriatal projections (Taber and Fibiger, 1995), and indirectly by an effect on mesolimbic dopaminergic neurons in the midbrain (Murase et al., 1993; Karreman et al., 1996). Simultaneous increase in dopamine and glutamate levels may indicate rTMS induced effects of glutamate on adjacent dopaminergic nerve terminals, mediated by local ionotropic or metabotropic glutamate receptors. Cortical glutamatergic neurons originating in the prefrontal cortex and dopaminergic neurons from the ventral tegmental area (VTA) synapse in close proximity to one another on the spines of nucleus accumbens medium spiny neurons (Sesack and Pickel, 1992). A modest increase in dopamine content has

also been shown in brain homogenates of striatal and hippocampal regions (Ben-Shachar et al., 1997), however, rTMS in this study was applied less focally compared to stimulation in microdialysis studies. Dopamine concentrations have also been found to increase in the striatum and the frontal cortex after ECT (McGarvey et al., 1993; Yoshida et al., 1998). In contrast, acute rTMS did not affect hippocampal noradrenaline release (Ben-Shachar et al., 1997; Keck et al., 2000b) as observed after ECT (Thomas et al., 1992) or extracellular homovanillic acid (HVA) and acetylcholine in the nucleus accumbens (Zangen and Hyodo, 2002).

Using *in vivo* microdialysis in rats Juckel et al. (1999) were able to demonstrate that focal electrical stimulation of the medial prefrontal cortex causes a release of serotonin (5-HT) in the hippocampus and amygdala (Juckel et al., 1999). Such a 5-HT release has not been observed in a microdialysis study after high frequency rTMS (20 Hz) of frontal regions in rats (Keck et al. 2000b). In contrast, a gradual increase of the serotonin metabolite 5-hydroxy-indoleacetic acid (5-HIAA) in the nucleus accumbens occurred after frontal and caudal low frequency rTMS (2 Hz) compared to sham stimulation (Zangen and Hyodo, 2002). While the increase in dopamine was observed only during rTMS in this study, the 5-HIAA levels continued to increase >60 min after the train. However, extracellular levels of 5-HIAA do not necessarily correlate with serotonin itself (Cumming et al., 1992). Findings showing a selective increase of 5-HT_{1A} binding sites in different frontal regions (Kole et al., 1999), a downregulation of 5-HT_{2A} receptors in the frontal cortex and striatum (Ben-Shachar et al., 1999) and rTMS-associated decrease of HT_{1A} and HT_{1B} autoreceptor sensitivity (Gur et al., 2000) offer additional evidence of rTMS action on serotonergic neurotransmission. Some of these findings coincide with changes observed after ECT and other antidepressant interventions (Zis et al., 1992; Gur et al., 1997; Gur et al., 2000; Post and Keck, 2001).

In animal models, frontal rTMS appears to have an effect on neurotransmitter systems which are involved in the pathophysiology of major depression. However, the comparison to prefrontal rTMS in humans is looked upon controversially (Lisanby et al., 2000) as rTMS in small rodents may be less focal due to constraints of rTMS coil sizes and differences in the functional anatomy of the prefrontal cortex between men and rodents.

Effects on functional neuroanatomy in humans

Brain imaging studies in depressed patients have consistently found abnormalities in the prefrontal cortex, cingulate gyrus, orbitofrontal cortex, or deeper limbic regions like the amygdala, insula and hippocampus which are often reversible after clinical recovery (see meta-analyses by Fitzgerald et al., 2006c; Steele et al., 2007). The first studies investigating rTMS in depression attempted to use cortical rTMS to interact with these interconnected brain regions. The first combination of rTMS and functional neuroimaging in real time was performed with fluorodeoxyglucose PET in a patient before and after rTMS treatment for refractory depression (George et al., 1995). Conclusions from this single case study were limited. However, it clearly demonstrated the potential of combining TMS with functional imaging to address clinical issues and understand what TMS is doing in the brain. There have now been many formal TMS studies with FDG PET. For example, a study of 1 Hz stimulation over the motor cortex for thumb showed decreased glucose uptake at the site of stimulation and in the contralateral motor cortex (Wassermann et al., 1997). Stimulation was performed at 1 Hz because FDG takes 20 min to settle into neurons and is thus a composite picture of brain activity over 20 min. This paradoxical decrease in localized brain activity at the mirror or contralateral site during TMS has been confirmed by electrophysiology (Chae et al., 2004). A similar study of slow (1 Hz) rTMS over the prefrontal cortex found that TMS, compared to a baseline or sham condition, was associated with global

reductions in blood flow, as well as localized reductions in activity in the left DLPFC (the TMS site), and connected regions such as the caudate, the orbitofrontal cortex bilaterally, and the cerebellum (Kimbrell et al., 2002). This work implies that prefrontal 1 Hz rTMS in normal adults has profound brain effects both locally and remotely, perhaps explaining some of the more interesting clinical and research findings in mood regulation, OCD, and working memory (Kimbrell et al., 2002).

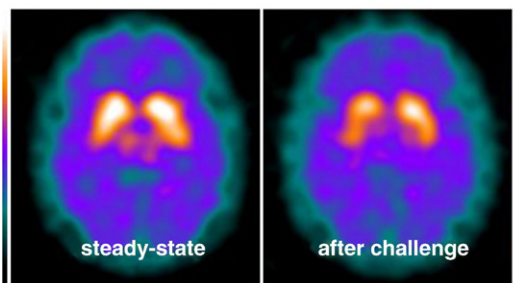
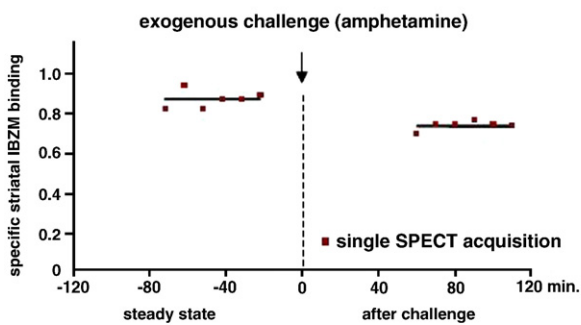
Another imaging tool that allows for tracer injection away from the camera is perfusion single photon emission computed tomography (SPECT) (George et al., 1991). In 8 healthy adults, George et al. used perfusion SPECT, which is taken up in 30–40 s, to image cerebral blood flow during fast (20 Hz) left DLPFC rTMS (George et al., 1999). Compared to a control scan with sham rTMS, they reported relative decreases under the coil site and in the anterior cingulate and orbitofrontal cortex. rTMS produced relative increases in blood flow in the brainstem and the cerebellum. Perfusion SPECT can only yield information about brain changes relative to other brain regions, not absolute brain activity. It is also unclear which period in relation to injection and scanning is precisely reflected by the image. The same group used SPECT to examine rTMS-related changes in depressed subjects undergoing a treatment trial, and found rTMS induced changes in limbic activity, particularly subgenual cingulate and orbitofrontal cortex, especially in rTMS responders (Teneback et al., 1999).

In a recent most interesting study with potential far-reaching implications for using rTMS in clinical treatment, Speer et al. (2008) used FDG- and H²¹⁵O-PET to scan depressed patients before and after 10 days of prefrontal rTMS treatment extending previous observations at 80% of resting motor threshold (RMT) intensity (Kimbrell et al., 1999) of differential responsivity to high vs. low rTMS frequencies within individual depressed subjects. There was a clear inverse relationship between degree of change on 1-vs. on 20-Hz rTMS within 19 depressed individuals. The overall magnitude of the clinical

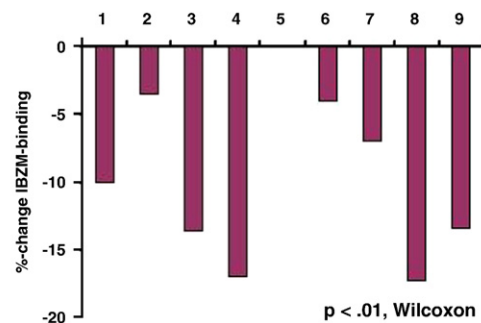
changes at 100% of RMT in this study were not, however, greater than those at 80% RMT in the first study (Kimbrell et al., 1999). Consistently, a previous study by the same group (Speer et al., 2000) investigated rCBF changes during rTMS treatment and found significant increases in rCBF across the group of all 10 patients that were located in the prefrontal cortex (L>R), the cingulate gyrus (L>>R), and the left amygdala, as well as bilateral insula, basal ganglia, uncus, hippocampus, parahippocampus, thalamus, and cerebellum. In contrast, 1-Hz rTMS was associated with a reduction of rCBF. Significant decreases in flow were noted in small areas of the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala. The changes in mood following the two rTMS frequencies were inversely related such that individuals who improved with one frequency worsened with the other. These data indicate that 2 weeks of daily 20-Hz rTMS over the left prefrontal cortex at 100% RMT intensity induce persistent increases in rCBF in bilateral frontal, limbic, and paralimbic regions implicated in depression, whereas 1-Hz rTMS produces more circumscribed decreases (including in the left amygdala). These data demonstrate frequency-dependent, opposite effects of high and low frequency rTMS on local and distant regional brain activity that may have important ramifications for clinical use of rTMS.

Another neuroimaging approach has focused on dopaminergic neurotransmission extending previous findings of rTMS induced dopamine release in animal experiments. In a landmark study, Strafella et al. used ligand PET and showed that TMS over motor cortex caused dopamine release in the ipsilateral caudate (Strafella et al., 2003). This study demonstrates the ability of focal electrical stimulation to cause sitespecific neurochemical changes in distant regions of the brain. This finding nicely converges with previous findings from animal studies (Keck et al., 2002) and was recently extended by a study of Pogarell et al. (2006, 2007) who found a reduction of iodobenzamide (IBZM) binding to striatal D2/D3

A Dynamic [¹²³I]-IBZM SPECT paradigm with challenge (3000 stimuli 10 Hz rTMS or 0.3 mg/kg d-amphetamine)



B Change of striatal [¹²³I]-IBZM-binding after rTMS



C Comparison of rTMS and d-amphetamine challenge

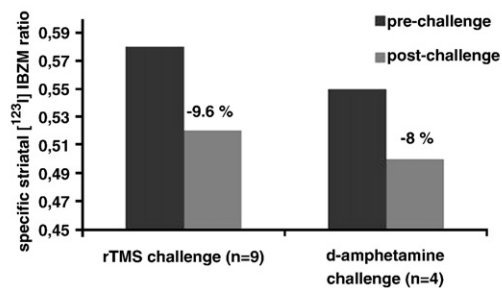


Fig. 1. Comparison of striatal dopamine release after d-amphetamine challenge (0.3 mg/kg) and left prefrontal rTMS (10 Hz, 3000 stimuli/session, 100% RMT) in a dynamic [¹²³I] iodobenzamide (IBZM) single photon emission computed tomography (SPECT) rTMS challenge paradigm modified from Laruelle et al. (1996) (A). After an exogenous dopaminergic challenge (d-amphetamine or rTMS) a reduction of the specific striatal IBZM binding was observed (Pogarell et al. 2006, 2007) (B). The mean reduction of specific IBZM binding was 9.6% after rTMS in 9 investigations (C). The reduction of IBZM binding after rTMS reached the same magnitude as the reduction after challenge with 0.3 mg d-amphetamine (D).

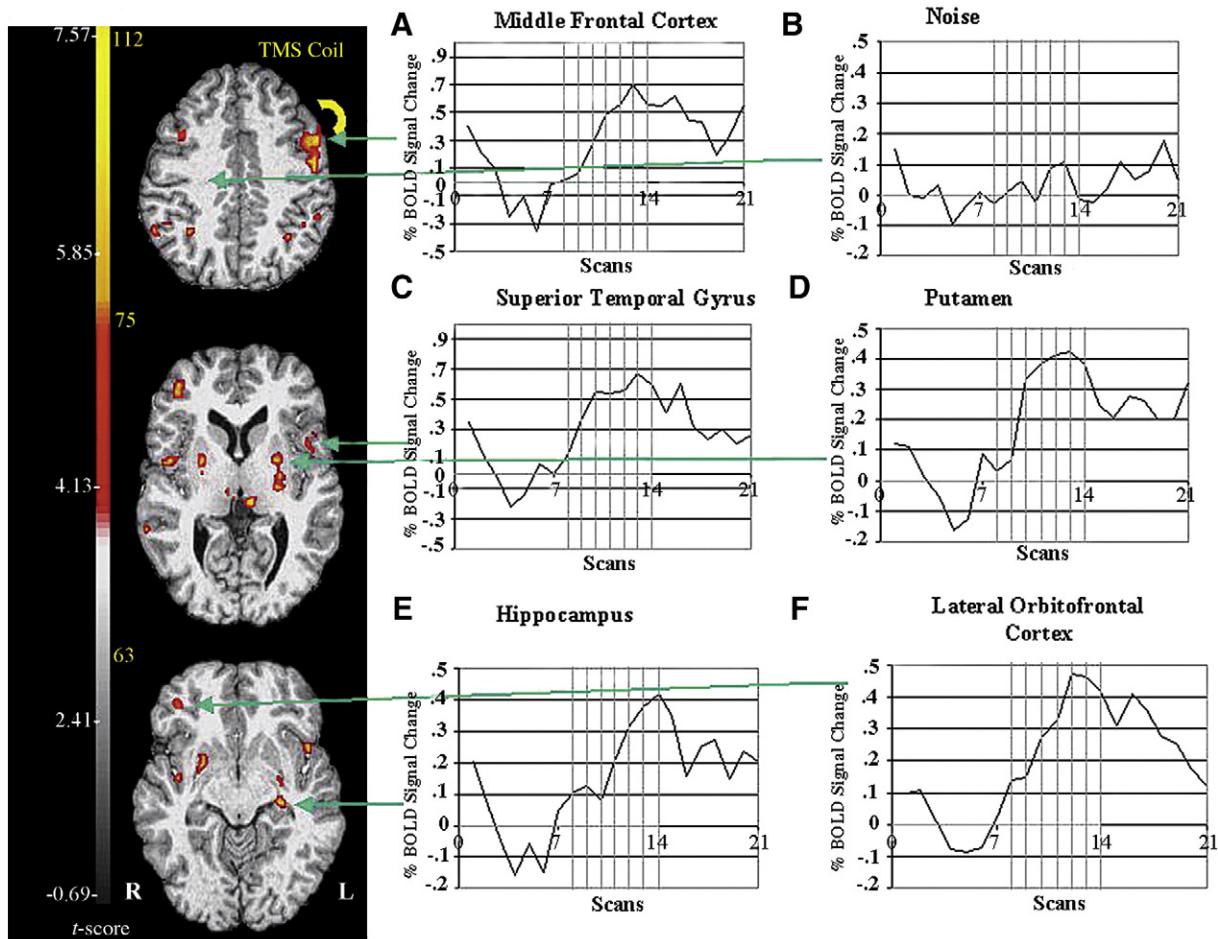
receptors in depressed subjects following a single session of 10 Hz rTMS of the left DLPFC. The effect size was comparable to the effect of a single dose of D-amphetamine on IBZM binding (Fig. 1).

A promising, but also technically challenging, imaging modality for rTMS is combining rTMS and functional MRI (fMRI). Bohning et al. first demonstrated the capability of interleaving rTMS and blood flow imaging (Blood Oxygen Level Dependent (BOLD) fMRI) with good spatial and temporal resolution (Bohning et al., 1998). Fig. 2 shows a group map of depressed subjects while being stimulated over the left prefrontal cortex, with areas of rTMS induced activation superimposed in color. Note that as the rTMS machine is alternately triggered at 1 Hz for 7 s and then is turned off, regional brain activity changes both underneath the coil, and in deeper limbic regions (Li et al., 2004a).

Targeting rTMS and neuronavigation

Can we position the TMS coil based on images of brain structure or function? One of the major problems confronting TMS research, especially when stimulating outside of primary motor or visual pathways, is trying to determine exactly where one is stimulating in the brain. In many TMS studies the placement of the TMS coil has been determined by referencing the stimulation a certain distance

from a functionally determined spot, such as the motor area for thumb, or by choosing an anatomical landmark (e.g. distance from the lateral canthus of the eye), or by using a variant of the EEG electrode placement system (Kahkonen et al., 2005) The current probabilistic approach to coil placement for depression treatment was developed and adopted initially in 1995 (George et al., 1996) Herwig et al. elegantly demonstrated the limitations of this approach (Herwig et al., 2001, 2003). In Fig. 3, a standard rTMS approach in depression is illustrated. Fig. 3C shows the individual Talairach coordinates before and after standard positioning of the coil that were visualized in an individual surface rendered brain MRI (white matter segmentation). In some individuals, particularly those with large skulls, or where their motor strip is posterior, the 5 cm rule results in stimulation of the premotor and not prefrontal cortex. Such standard positioning approaches serve to standardize TMS placement, but it is well known that different individuals have widely varying brain sizes and morphology. In addition to differences in brain structure, the functional location of behaviors varies even more across different individuals, especially for behaviors other than simple movement or vision. Thus in general, except for motor and visual studies where external monitoring of TMS effects may be possible, researchers have struggled to invent better methods for positioning the TMS coil.



Cluster analysis uses *t* threshold = 3.85, cluster *p* < .05; *n* = 14

Fig. 2. These are transverse images of MRI scans at different depths. Superimposed in color are the brain regions that were significantly activated during left prefrontal TMS in 9 medication free depressed patients. Note the activation in the left (right side of image) prefrontal cortex, directly underneath the coil. Also note the increased activation in other connected areas, including the orbitofrontal cortex and insula. Imaging studies such as this one demonstrate that rTMS has both an immediate local effect directly under the coil, as well as secondary effects in connected regions. From Li et al., 2004a. Reprinted with permission.

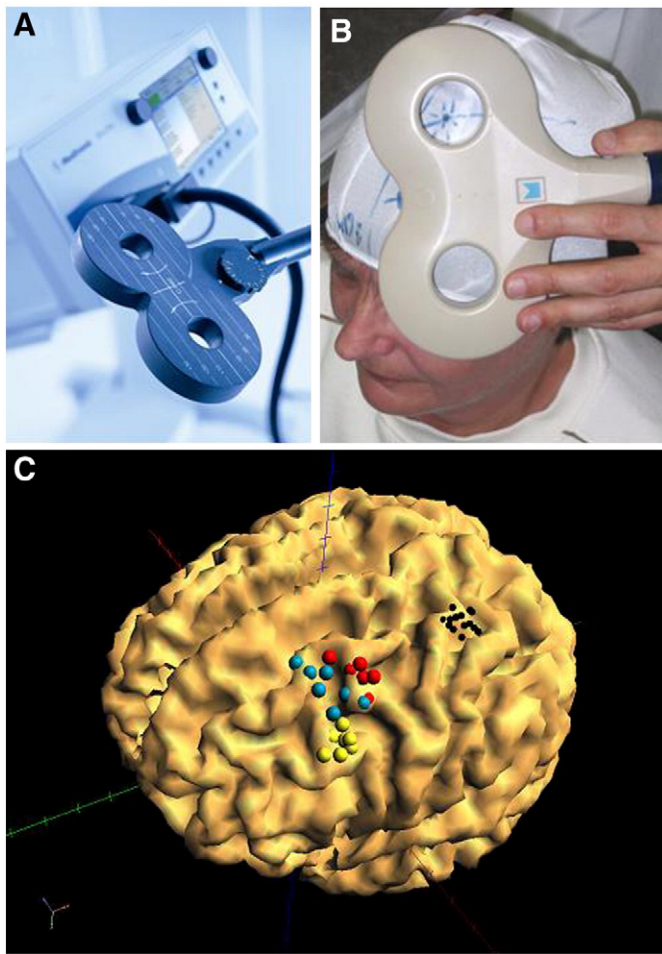


Fig. 3. (A) rTMS of the dorsolateral prefrontal cortex. In the majority of studies rTMS has been applied in repeated sessions (1000 to 3000 stimuli/d) once daily during working days and the total duration of treatment has varied between 2 and 6 weeks. (B) The most common coil position targets the left dorsolateral prefrontal cortex by measuring 5 cm anterior (on the skull surface) to the optimal position for evoking a motor evoked potential in hand muscles. However, a considerable variability occurs with this approach, as demonstrated in a study applying neuronavigated rTMS (Herwig et al., 2001). The small black dots indicate the optimal sites for abductor pollicis brevis muscle stimulation over the motor cortex i.e. the region around the lateral edge of the hand knob. The larger dots indicate the rostral coil positions over the different Brodman areas: blue BA 6, red BA 6/8 and 8, yellow BA 8/9 and 9. Talairach coordinates before and after “standard positioning” of the coil are visualized in an individual surface rendered MRI of the brain (white matter segmentation), which was transformed into Talairach space. Reprinted from *Biological Psychiatry* Vol. 50; Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of “standard” coil positioning by neuronavigation; pp. 58–61; Copyright (2001), with permission from Elsevier Science.

In a very important “proof of concept” study, Fitzgerald et al. (2009) provided first evidence that rTMS targeted to a spot between the center of BA 9 and the border of BA 9 and 46 defining a key region within the DLPFC is superior in terms of antidepressant efficacy compared to standard coil positioning (random groups of 24 vs. 27 patients). There are currently several different systems for positioning a TMS coil based on a subjects’ structural MRI scan. However, it is unclear at present how necessary this degree of coil positioning is for many TMS research and clinical applications. As mentioned above, gyral anatomy and morphology vary a great deal between individuals. Additionally, it is not trivial to agree on specific gyri across individuals. Finally, as noted above, the location of different functions within distinct cortex regions also varies. So even stimulating the same anatomical spot across individuals does not

guarantee that one is stimulating the same or a functionally equivalent region.

Whether one day the clinical application of rTMS will require individual MRI-guided neuronavigation is not clear. An important unanswered question to be addressed over the next decade is whether there are specific regions of the prefrontal cortex that might prove more effective for rTMS as antidepressant intervention. For example, one may assume that stimulation over a gyrus would be more clinically effective than placement over a sulcus. Equally important is whether stimulation over distinct Brodman regions, or key regions within the prefrontal cortex (medial, lateral, anterior, etc), are more effective than others. It is likely that more sophisticated and flexible approaches to coil positioning and individual adjustment will be needed to optimize TMS as a treatment for depression and other neuropsychiatric illnesses.

Clinical trials in depressed patients

To date, more than 35 individual randomized, placebo-controlled clinical trials including over 1200 patients suffering from major depressive episodes have been conducted investigating the safety and efficacy of rTMS as an antidepressant intervention. In the majority of these trials, significant placebo/verum differences have been observed with antidepressant effects ranging from modest to substantial. Due to the methodological limitations of many of these trials which had rather small sample sizes, difficulty with controlling placebo rTMS and short observation periods, the current assessment of its efficacy is more sober after initial enthusiasm about its treatment potential. Several meta-analyses (Table 1) have been conducted (Holtzheimer et al., 2001; McNamara et al., 2001; Burt et al., 2002; Martin et al., 2003; Couturier, 2005; Herrmann and Ebmeier, 2006) supporting the antidepressant efficacy of rTMS, but the clinical effect sizes are modest and the clinical significance may be questionable. A recent meta-analysis (Herrmann and Ebmeier, 2006) included 33 individual trials with 877 patients and found rTMS to be more effective than sham rTMS, with a large effect size of 0.71. The average reduction of depression scores after active rTMS was 33.6% compared to 17.4% after sham rTMS. As trials showed a substantial variability it was not possible to identify a distinctly efficacious protocol that was clearly better than others. This was in contrast to a previous descriptive review (Gershon et al., 2003) that suggested several patient factors and treatment parameters predicting a better clinical outcome of rTMS. However, mean effect sizes were reduced, although still significant, in studies with stimulation intensity below 90% of motor threshold and new medication starting within ± 7 days of start of TMS (Herrmann and Ebmeier, 2006).

Differential use in the depression spectrum

Although there is general evidence of rTMS exerting antidepressant effects it is important to emphasize that each specific application of rTMS in depressive disorders requires trials specifically designed to test the respective hypothesis. The following sections will address such specific applications.

rTMS combined with antidepressant pharmacotherapy as first-line intervention

New antidepressant treatment strategies that promise to speed up and increase primary response rates in depression are of great interest. Several studies have addressed this question in a placebo-controlled manner and combined HF rTMS treatment with SSRIs, TCAs and novel acting agents. Garcia-Toro et al. (2001a) and Lisanby et al. (2002) failed to show a significant difference between active rTMS and sham rTMS, each combined with sertraline for a treatment period of 2 weeks. Similarly, Hausmann et al. (2004a,b) did not observe a

Table 1
Overview on meta-analyses of controlled studies investigating rTMS in depression.

Meta-analysis	N_{trials}	$N_{\text{pat.}}$	Comparison of rTMS parameters	Comparison of MD subtypes	Effect sizes	Conclusions
McNamara et al., 2001	5	81	No	No	NNT 2.3*	Beneficial effects in depression Real rTMS statistically superior to sham rTMS, Statistically robust effect favoring real rTMS, effect sizes heterogeneous Low quality trials, insufficient evidence
Holtzheimer et al., 2001	12	ND	Yes (site)	No	WMD = 0.81/0.89*	
Burt et al., 2002	16	377	Yes (LF vs. HF rTMS)	No	$d_{\text{pooled}} = 0.67^*$	No significant difference between real and sham rTMS, low power of trials Real rTMS more effective than sham rTMS, great variability and no significant predictors either due to insufficient power or to non-specific treatment effects
Martin et al., 2003	12	217	Yes (site and frequency)	No	SMD = -0.35* (left HF rTMS, only after 2.2 weeks)	
Couturier, 2005	6	91	only left prefrontal HF rTMS, no	No	WMD = -1.1, n.s.	
Herrmann and Ebmeier, 2006	33	877	only left prefrontal HF rTMS, Yes (intensity, frequency, number of stimuli)	No	$d_{\text{pooled}} = 0.71^*$	

* Statistically significant difference between real and sham rTMS.

significant difference between different active rTMS approaches and sham treatment combined with citalopram, milnacipram, mirtazapine or reboxetine for a 2 week period. More recently, Rumi et al. (2005) successfully combined 5 Hz left prefrontal rTMS with amitriptyline which was started 7 days prior to the course of rTMS treatment in 46 patients. The total treatment was longer (4 weeks vs. 2 weeks) compared to previous studies. Rossini et al. (2005) reported superior efficacy of 15 Hz left prefrontal rTMS combined with venlafaxine, sertraline or escitalopram compared to sham rTMS, however, the large effect size observed in this study was out of the range of effect sizes found in comparable trials (Herrmann and Ebmeier, 2006). More recently, a multicenter trial funded by the German Research Foundation investigated another combined treatment strategy (Herwig et al., 2007). 127 patients with moderate to severe major depressive episodes were recruited at seven study sites. The patients were newly started on antidepressant treatment with either mirtazapine or venlafaxine following a standardized titration protocol. Simultaneously, patients were randomized to active or sham rTMS (10 Hz, 110% motor threshold intensity, 2000 stimuli per day), and treated for 3 weeks with a 3 week follow-up period. After 3 weeks, response rates in both treatment groups were about 30% and only after follow-up there was a slight superiority of active treatment (58% after real rTMS vs. 47% after sham rTMS), which did not reach statistical significance. Thus, the question is still not answered, whether rTMS may be useful in combination with other antidepressant interventions. Also non-pharmacological approaches are of interest in this respect, e.g. rTMS

has been used to extend the treatment effects of partial sleep deprivation for several days (Eichhammer et al., 2002).

rTMS in therapy-resistant depression

rTMS was originally suggested to be a potential substitute for electroconvulsive therapy (ECT). Therefore the majority of previous trials has been conducted in rather pharmacotherapy-resistant or even refractory patients (Pascual-Leone et al., 1996; George et al., 1997a,b; Klein et al. 1999; Padberg et al., 1999; Eschweiler et al., 2000; Berman et al., 2000; George et al., 2000; Garcia-Toro et al., 2001b; Boutros et al., 2002; Padberg et al., 2002; Loo et al., 2003; Manes et al., 2001; Miniussi et al., 2005; Fitzgerald et al., 2006; Avery et al., 2006). Though treatment-resistant patients show lower response rates to any antidepressant intervention compared to non-treatment-resistant subjects, controlled trials in this patient group may have the advantage that placebo response rates are also reduced. This may allow to demonstrate placebo-verum differences at rather small sample sizes. Whereas most investigators applied rTMS as add-on treatment to a stable medication, fewer trials have focused on medication-free patients who then underwent rTMS monotherapy (George et al., 2000; Manes et al., 2001; O'Reardon et al., 2007).

Aside from differences in patient characteristics, a major confounding factor for the varying effect sizes could be the huge variation of stimulation parameters across studies. Dosing parameters of rTMS are comprised not only of a daily dosage but of a larger number of

Table 2
Trials comparing high frequency rTMS of the left dorsolateral prefrontal cortex and ECT in depressed subjects.

Study	Design	Behandlungs-gruppe	N	Age [yrs]	Diagnosis	Therapy resistance	Reduction of HAMD scores
Grunhaus et al., 2003	Parallel, randomized	10 Hz rTMS	20	58.4	MD (21 psychotic)	5	40.3%*
		ECT	20	63.6		10	60.6%*
Pridmore, 2000	Parallel, randomized	20 Hz rTMS	16	44.0	26 UP6 BP	All	55.6%
		ECT	16	41.5			66.4%
Janicak et al., 2002	Parallel, randomized	10 Hz rTMS	14	42.9	17 UP8 BP (9 psychotic)	All	55%
		ECT	11	42.7			64%
Grunhaus et al., 2003	Parallel, randomized	10 Hz rTMS	20	57.6	MD (non-psychotic)	All	45.5%
		ECT	20	61.4			48.2%
O'Connor et al., 2003	Parallel, non-randomized	10 Hz rTMS	14	51.2	MD (non-psychotic)	nr	12.7%*
		ECT	14	48.4			60.8%*
Schulze-Rauschenbach et al., 2005	Parallel, non-randomized	10 Hz rTMS	16	47.7	MD (non-psychotic)	All	39%
		ECT	14	46.7			35%
Rosa et al., 2006	Parallel, randomized	10 Hz rTMS	21	41.8	MD (non-psychotic)	All	≈40%
		ECT	21	46.0			≈41%
Eranti et al., 2007	Parallel, randomized	10 Hz rTMS	24	63.6	42 UP	All	22%*
		ECT	22	68.3	4 BP (7 psychotic)		58%*

Grunhaus et al. (2000), O'Connor et al. (2003) and Eranti et al. (2007) observed a significant difference (*) between treatment conditions favoring ECT, the other studies did not show a statistical significant difference between groups.

Abbreviations: MD = major depression; UP = unipolar; BP = bipolar; HAMD = Hamilton Rating Scale for Depression; nr = not reported.

parameters including frequency, intensity, stimulation site, number of stimuli, duration of treatment, etc. All of these may influence the rTMS-mediated antidepressant effect. Several studies have attempted to compare two active conditions (Pascual-Leone et al., 1996; Padberg et al., 1999; George et al., 2000; Padberg et al., 2002; Fitzgerald et al., 2003; Fitzgerald et al. 2006a, e.g. Fitzgerald et al. (2006) compared two LF frequencies (1 Hz vs. 2 Hz) in a larger sample of 130 subjects and did not observe a difference in terms of therapeutic efficacy.

Fitzgerald et al. (2003) were the first directly comparing left HF rTMS and right LF rTMS with sham treatment. Both real rTMS groups improved significantly over 2 weeks compared to the sham rTMS group and improvement was continued if subjects underwent real rTMS during weeks 3 and 4. Thus, this study provided support for extending the rTMS treatment period in order to increase response and remission rates. Avery et al. (2006) reported data of 68 patients with medication-resistant major depression with a response rate of 31% (vs. 6% after sham rTMS) and a remission rate of 20% (vs. 3% after sham rTMS) after 15 sessions of 10 Hz rTMS during a 4-week period.

A very recent international multicenter trial compared real and sham rTMS in a large sample of 301 outpatients (23 trial sites) suffering from a major depressive episode (O'Reardon et al., 2007). All patients were medication-free during the trial. The treatment was conducted using an iron core coil at aggressive stimulation parameters (120% RMT intensity or highest tolerable dosage, 10 Hz, 3000 stimuli/d) and extended for up to 6 weeks. HRSD scores rapidly declined during the first two weeks and significantly differed between groups after 4 and 6 weeks of treatment. Response rates were 19% after 4 weeks of real rTMS (vs. 12% after sham rTMS, significant) and 24% (vs. 15%, significant) after 6 weeks and the respective remission (HRSD₂₄ < 11) were 9% (vs. 8%, not significant) after 4 weeks and 17% (vs. 8%, significant) after 6 weeks.

Several research groups have investigated whether rTMS reaches the high efficacy rates seen with ECT (response rates between 60 and 90%). These comparative studies are listed in Table 2. Grunhaus et al. (2000), O'Connor et al. (2003) and Eranti et al. (2007) observed a significant difference between treatment conditions favoring ECT, whereas the other studies did not show a statistical significant difference between groups. Interestingly, Grunhaus et al. (2000) reported that ECT was clearly superior to rTMS in the overall group and in patients with psychotic depression, but rTMS reached the efficacy of ECT in the subgroup of non-psychotic patients. Consistent with this finding is that the most robust body of evidence regarding an action of rTMS on neurotransmission points to an action on the dopaminergic system resulting in dopamine release in mesostriatal and possibly mesolimbic regions. This converges with the recent discussion regarding the role of dopamine in major depression and the use of dopaminergic agents (e.g. bupropion and amineptine) in treatment-resistant depressive states.

A few groups have investigated whether more intense or novel stimulation protocols exhibit an enhanced antidepressant efficacy in therapy-resistant patients (Loo et al., 2003; Hausmann et al., 2004a; Fitzgerald et al., 2006b). Two of these studies failed to find enhanced efficacy of bilateral rTMS (left prefrontal HF combined with right prefrontal LF rTMS – Hausmann et al. 2004a and bilateral prefrontal HF rTMS – Loo et al., 2003). In contrast, Fitzgerald et al. (2006b) found a clinically meaningful effect of combined left prefrontal HF (10 Hz, 750 stimuli/d) and right prefrontal LF (1 Hz, 420 stimuli/d) rTMS superior to sham rTMS. However, there was no comparison with a standard unilateral rTMS.

Currently, longer treatment periods are suggested extending the 1–2 weeks treatment in the early studies to 4–6 weeks protocols (Grunhaus et al., 2000; Fitzgerald et al., 2003, 2006a). More recently, Fitzgerald et al. (2008) investigated in 60 patients whether the efficacy of right prefrontal 1 Hz rTMS could be increased by a 6 Hz subthreshold priming stimulation and observed that patients undergoing priming rTMS had a more favorable outcome than did patients

receiving sham priming. In summary, evidence from numerous small trials, meta-analyses and one large RCT support the use of rTMS in depressed subjects who exhibit a moderate degree treatment resistance.

rTMS in bipolar depression

Management of depression in the context of bipolar disorders constitutes a major clinical problem. Although antidepressant properties have been reported, mood stabilizers such as the anticonvulsants carbamazepine and valproic acid are not particularly effective in depressed phases of the disorder. Lamotrigine, an anticonvulsant, does appear to have some antidepressant effects. The use of conventional antidepressant medication during the depressed phase may counterproductively increase a patient's cycle frequency. In several studies investigating the efficacy of rTMS in major depressive episodes also bipolar patients had been included. However, separate data have not been available in this patient group and switches to manic states have been reported in bipolar patients undergoing rTMS (Ella et al., 2002). A first study of rTMS in bipolar depression Dolberg et al. (2002) compared active and sham rTMS in 20 patients. A significant difference between both groups was apparent after 2 weeks and lost after 4 weeks. Due to the lack of a more detailed description of the patients sample and additional interventions, these data are difficult to interpret. Nahas et al. (2003) applied rTMS in 23 depressed bipolar patients (12 diagnosed as BPI in a depressed state, 9 as BPII in a depressed state, 2 as BPI in mixed states). There was no statistically significant difference between both groups regarding the clinical outcome (at least 50% reduction of baseline HRSD scores or an HRSD score < 10 – 4 active and 4 sham) or the mean HRSD change from baseline over 2 weeks. Compared to sham rTMS, active rTMS produced a trend but no statistically significant greater improvement in daily subjective mood ratings after treatment. Interestingly, 7 patients of this acute study were followed during weekly maintenance treatment with rTMS for up to one year (Li et al., 2004b). Three subjects completed the full one year period and preserved an average HRSD score of 13 during the whole period. Though rTMS is an acute intervention compared to VNS or DBS, maintenance strategies may be clinically important and should be differentially tested in future trials.

rTMS in co-morbid depression

Repetitive TMS treatment might have a therapeutic benefit not only for major depression, but also for depression associated with neurological disorders, such as Parkinson's disease (PD) and stroke. Although depression in neurological conditions is associated with a significant impact on quality of life, it is poorly managed and one of the main reasons is the lack of satisfactory therapies as antidepressants are often inadequate due to side effects and drug interactions. There are two main advantages for using rTMS for the treatment of depression in neurological disorders: (i) rTMS is associated with few adverse events (see review by Machii et al., 2006). In contrast to antidepressants, rTMS does not interact with drugs commonly used for the treatment of neurological disorders. This is particularly important for PD patients that usually take several medications that have drug interactions with antidepressants; and (ii) rTMS may simultaneously ameliorate the underlying neurological disease and psychiatric symptoms. For instance, rTMS treatment for depression in PD patients has been reported to improve mood and motor function simultaneously (Dragasevic et al., 2002).

Initial studies have been conducted to evaluate the antidepressant effects of rTMS in PD (Dragasevic et al., 2002; Fregni et al., 2004) and stroke (Jorge et al., 2004, 2008); and, in addition, rTMS treatment could potentially be a helpful therapeutic alternative for depression in epilepsy and Alzheimer's disease. Two studies have explored the question of whether rTMS treatment for depression in PD is effective.

The first open trial by Dragasevic et al. (2002) showed that bilateral LF rTMS of the left and right prefrontal cortex result in a significant improvement of depression and motor function. After this study, Fregni et al. (2004) performed a randomized, double-blind, controlled study to evaluate the effects of HF rTMS on mood in patients with PD. This study showed that 10 consecutive sessions of rTMS exert an antidepressant effect comparable to the effect of fluoxetine treatment. This study also showed a cognitive improvement after rTMS that was further explored by Boggio et al. (2005).

Promising results were obtained for the treatment of depression in stroke. Jorge et al. (2004) showed that 10 sessions of active rTMS (10 Hz, 110% of the motor threshold) reduced depressive symptoms compared to sham stimulation, and were associated with a trend towards cognitive improvement. Recently, the same group (Jorge et al., 2008) has published a placebo-controlled replication study. After discontinuation of antidepressants, 92 patients with clinically defined vascular depression were randomly assigned to receive active or sham rTMS of the left DLPFC. Patients underwent rTMS at two different dosages (12 000 – experiment 1 – or 18 000 pulses – experiment 2 – totally). In experiment 1, a 33.1% reduction of HRSD scores was found after active rTMS compared to 13.6% after sham rTMS. Similarly, experiment 2 showed a 42.4% reduction after active compared to 17.5% after sham treatment. Whereas response and remission rates did not significantly differ in experiment 1, they showed significant differences between groups in experiment 2 (response rates: 39% after active vs. 6.9% after sham rTMS, remission rates: 27.3% after active vs. 3.5% after sham rTMS). Finally, because rTMS has been shown to decrease the frequency of seizures (Fregni et al., 2005) and also induces a significant improvement in some aspects of cognition in patients with major depression (Moser et al., 2002), it is conceivable to hypothesize that this therapy might be suited to treat depression in epilepsy and in dementia syndromes, such as Alzheimer's disease. Further trials need to evaluate the clinical utility of rTMS for the treatment of depression in these neurological conditions.

Variables predicting response to rTMS treatment

It remains an important issue to identify those features of the depressive syndrome that predict a response to rTMS (Gershon et al., 2003; Loo and Mitchell, 2005). Besides a few small studies having included secondary analyses addressing the predictor question (Conca et al., 2000; Holtzheimer et al., 2004; Bajbouj et al., 2005), four recent studies explicitly focused on investigating predictors of antidepressant response to rTMS based on patient and treatment characteristics: in a large multicenter analysis of Fregni et al. (2006), data from 6 clinical trials performed at different institutions were pooled leading to a sample of 195 depressed patients. Regression models were applied to analyze whether demographic, depression and treatment characteristics as well as psychiatric and drug history were associated with antidepressant response. Multivariate analyses showed that only age and therapy resistance were significant negative predictors of improvement even after adjusting these variables for other significant predictors or potential confounders (like study site). In another recent predictor study (Brakemeier et al., 2007), predictors of antidepressant response were analyzed in a logistic regression analysis of 70 depressed patients testing the predictive value of HAMD factors (Milak et al., 2005), CORE criteria of psychomotor change (Hadzi-Pavlovic et al., 1993), and other clinical characteristics. Again, a low level of therapy resistance, a short duration of episode, and a high level of sleep disturbances were positive predictors of improvement during rTMS. Very recently, parameters predicting the therapeutic response to high frequency rTMS of the left DLPFC were studied in a homogenous sample of 79 non-medicated depressed patients (Brakemeier et al., 2008). While previous models of Fregni et al. (2006) and Brakemeier et al. (2007) were not replicated, an exploratory model with a satisfactorily fit showed that patients with a higher level of

therapy resistance, depressed mood, and feeling of guilt were less likely to benefit from rTMS whereas patients with a high level of retardation were more likely to profit from the treatment. The better response of patients with a high level of psychomotor retardation nicely converges with findings in animal models and studies in humans showing that prefrontal rTMS leads to an increase of dopaminergic neurotransmission in mesostriatal and mesolimbic regions (Keck et al., 2002; Pogarell et al., 2006). The fourth study by Lisanby et al. (2009) is based on the analysis of data from the international multisite trial by O'Reardon et al. (2007) including follow-up. The main finding was that rTMS was much more effective in patients who have failed to respond to one adequate trial of antidepressant medications in the current episode corresponding to a large effect size of 0.83, whereas the effect size for the subset of patients who failed 2–4 trials was 0.42. Thus, taking these findings together, a lower level of therapy resistance seems to be the only robust positive predictor of response to rTMS to date.

Limitations I: double-blind designs and sham control

Most investigators have applied modified double-blind protocols keeping the patient and the rater blind to treatment conditions. The person operating the stimulator is aware of the condition, but he is usually instructed to minimally interact with the patient to prevent any impact on the course of disease. The placebo condition itself has been developed over time. The vast majority of studies has used a sham condition where the coil is angled by 45° to 90° from the scalp. This sham condition has been turned out to be critical in two respects: 1. Somatosensory artefacts are much weaker than in the active condition and the patient may become aware of the difference either having a direct comparison with active stimulation in crossover trials and after motor threshold determination or by talking with other patients about their treatment 2. The sham condition where the coil is positioned at an angle of only 45° has turned out to be actually a weak active condition (Loo et al., 2000). Thus, many investigators have tried to design a sham coil that produces more noise, heating or tactile artefacts in order to mimic active rTMS. The most recent advances were made by combining sham rTMS with weak electrical stimulation of the scalp to generate a somatosensory artefact comparable with active rTMS (Rossi et al., 2007). Though mainly discussed for therapeutic trials, the problem of ineffective sham conditions and the lack of control for the potential non-specific effects of somatosensory scalp stimulation on outcome measures generally applies to experimental and clinical studies in rTMS research.

Limitations II: duration of effects and maintenance

It remains to be clarified, whether subsequent antidepressant treatment is necessary to stabilize the clinical response after rTMS. A deterioration of depressive symptoms within three weeks after one week of rTMS treatment was already reported by Pascual-Leone et al. (1996). Schuele et al. (2003) conducted a follow-up study on drug-free patients participating in an open rTMS trial over two weeks. They received 10 rTMS sessions (10 Hz, left prefrontal stimulation at 100% motor threshold intensity) and subsequent standardized antidepressant medication with mirtazapine (either monotherapy or combined with carbamazepine or lithium) for further four weeks. The interval between the last rTMS and the first day of pharmacotherapy varied between one and five days. A significant increase in the HRSD score of rTMS responders was observed during treatment interruption after rTMS. Moreover, there was a correlation between the length of the interval without treatment and the degree of deterioration. With subsequent mirtazapine treatment this deterioration subsided and the further clinical course was stabilized. This corresponds to the outcome in the combined dexamethasone suppression/CRH test, which suggests a high risk of relapse after clinical improvement, i.e. an effect

of rTMS on post-dexamethasone ACTH and cortisol levels, but no effect on the corticotropin releasing hormone-induced ACTH or cortisol increase (Zwanzger et al., 2003) suggesting a higher risk for a relapse after improvement of depressive symptoms.

Maintenance treatment with rTMS has been used successfully in single patients and open trials showing favorable long-term outcomes after maintenance protocols with 0.5–2 rTMS sessions/week. However, there is still a lack of systematic research on this issue and maintenance rTMS is more laborious than many other treatment strategies.

Safety

The notion that rTMS is safe and well tolerated by patients within a range of parameters defined according to a consensus (Wassermann, 1998), can be substantiated by an extensive body of data. After 10 days of daily prefrontal rTMS in depressed patients there was no sign of structural changes on MR scans (Nahas et al., 2000). There was no deterioration in neuropsychologic performance, no significant mean changes in auditory threshold, and no significant EEG abnormality after 2 to 4 weeks of rTMS shown in safety studies (Padberg et al., 1999; Loo et al., 2001; Moser et al., 2002; Martis et al., 2003; Hausmann et al., 2004b; Avery et al., 2006; Jaruel et al., 2006). Thus, there seem to be no adverse effects on cognition as observed after ECT.

On the basis that exclusion criteria are fulfilled (e.g. implanted electronic devices, previous history of seizures, etc.), meaningful side effects are physical discomfort on the scalp during and headache after rTMS. Moreover, rare single cases of rTMS-associated seizures have been reported since 1998 when safety guidelines were published limiting stimulation parameters (Wassermann, 1998; Conca et al., 2000). The risk of a seizure may be increased by both a long train duration, short intertrain intervals and concomitant medication. However, these cases have to be regarded in the light of many thousands of subjects who underwent rTMS to date. A very recent overview of published rTMS trials also including systematically collected safety data from a leading brain stimulation laboratory in the U.S. concluded that rTMS to non-motor areas appears to be safe with few, generally mild adverse effects (Machii et al., 2006). Whereas cognitive side effects have been monitored throughout experimental and therapeutic rTMS applications and are believed to be transient and short-lived, some patients have reported psychological and behavioral side effects in therapeutic trials (mostly in patients with affective disorders).

Treatment-emergent mania (TEM) has been reported for low and high frequency rTMS in patients with uni- and bipolar depression (Xia et al., 2008). Though single cases suggest a causal relationship between rTMS and TEM, the overall rate across 53 randomized controlled studies in depression appears to be low (0.84% TEM for active rTMS vs. 0.73% for sham rTMS) and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3 to 3.45%) (Xia et al., 2008). Similarly, cases of rTMS induced psychotic symptoms, anxiety, agitation, suicidal ideation and insomnia (Zwanzger et al., 2002; Janicak et al., 2008) have been reported, but it is unknown whether these occur at higher rates compared to the natural course of disease or associated with other interventions. Nevertheless, patients undergoing rTMS should be informed about these risks.

Conclusions

In addition to its established position as an experimental research tool in neuroscience, rTMS has been proven to exert antidepressant effects superior to placebo treatment, though the effect sizes are moderate and the clinical placement among pharmacological and non-pharmacological treatment options for depression is still a matter of debate. However, the recent evidence from a large international multicenter trial supporting the antidepressant efficacy of rTMS in

therapy-resistant depression has led to approval of rTMS by the U.S. Food and Drug Administration (FDA) in October 2008 for the treatment of depressed subjects who do not primarily respond to antidepressant medication. This approval will presumably stimulate a wider use of rTMS in clinical practice. For investigating other clinical applications of rTMS in affective disorders specific study designs are required or even need to be developed. Moreover, recent methodological developments as novel stimulation protocols (e.g. theta burst stimulation, Grossheinrich et al., 2009), new stimulation coils (e.g. H coils) and the combined application of rTMS together with transcranial direct current stimulation (tDCS) provide promising avenues for further enhancing the therapeutic efficacy of rTMS.

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