The Use of rTMS in Other Psychiatric Disorders

10

10.1 Introduction

As has been described in previous chapters, rTMS can have powerful effects on the brain. These effects can be neurophysiological (e.g. altering inhibition and plasticity), clinical (e.g. improvement of symptoms in patients with treatment-resistant depression) and cognitive (i.e. transient cognitive lesions, cognitive enhancement). As well as the development of rTMS methods for depression, in the last two decades there has been significant investigation into the treatment of numerous other psychiatric and neurological disorders. Whilst a comprehensive review of all of these findings is beyond the scope of this chapter, we will focus on psychiatric disorders in which initial evidence exists for the clinical utility of rTMS approaches or in which there has been particular therapeutic interest.

10.2 Mania

Due to the promising therapeutic effects of rTMS in depression, interest in the use of the treatment for mania developed early. In an initial study, 16 patients were randomised in a controlled trial of right versus left high-frequency (20 Hz) prefrontal stimulation [1]. Greater therapeutic benefits were seen with right-sided stimulation compared to left-sided stimulation, an observation that has been subsequently used to support notions of left and right-sided laterality activity differences in depression and mania. The therapeutic possibilities with high-frequency right-sided stimulation were also supported in two subsequent case series [2, 3].

However, data from sham-controlled trials is not consistent. In the first of these studies involving 25 patients, no difference between active and sham stimulation was seen [4]. However, in a recent study of 41 patients, a significant benefit of active over sham 20 Hz stimulation was seen with stimulation over a 10-day period [5].

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10.2.1 Summary

A limited body of research suggests that high-frequency stimulation applied to the right DLPFC may have some anti-manic effects, but this treatment needs to be more systematically evaluated.

10.3 Anxiety Disorders

10.3.1 Obsessive-Compulsive Disorder (OCD)

There is a compelling argument for evaluating the use of rTMS in obsessive-compulsive disorder (OCD). OCD can be highly disabling and patients with OCD often respond poorly to psychotherapy and/or serotonergic antidepressants, the standard forms of treatment. Moreover, unlike MDD which responds well to ECT, there is little to no evidence for therapeutic improvement of OCD with ECT. There is also a compelling mechanistic link between treatment mechanisms linked to rTMS and those mechanisms that are aberrant in OCD. For example, rTMS has been reported to potentiate GABAergic neurotransmission, particularly at high frequencies [6, 7]. rTMS can also modulate NMDA neurotransmitter mechanism [8] both of which have been associated with dysfunction in OCD [9, 10]. As such, not only is there an urgent need for newer treatments in OCD, but rTMS may target putative mechanisms in the cortex that are associated with OCD pathophysiology.

Greenberg et al. initially explored the efficacy of rTMS for OCD [11]. Twelve patients received 20 Hz rTMS at 80 % of the motor threshold to the right or left lateral prefrontal cortex or a control site. Right prefrontal stimulation decreased compulsions and improved mood to a greater degree than left-sided stimulation or control site stimulation. Several studies that have subsequently explored high-frequency stimulation applied to the left DLPFC have reported disappointing results [12, 13], but follow-up studies exploring high-frequency right-sided stimulation have not been systematically conducted.

Several studies have explored low-frequency approaches, generally without positive effects. For example, Alonso et al. reported the effects of 1 Hz rTMS applied to the right DLPFC over eighteen 20-min daily sessions [14]. There were no significant effects on obsessions or compulsions reported. Prasko et al. also used 1 Hz stimulation but applied to the left DLPFC [15]. They also failed to find therapeutic effects. One final study did suggest therapeutic effects of 1 Hz stimulation but applied in this case to the left orbitofrontal cortex [16]. Sixteen patients received active stimulation and seven patients received sham stimulation. They reported a significant difference between active and sham treated for up to 10 weeks after rTMS was completed.

A novel and promising approach has adopted a significantly different target, the bilateral supplementary motor area. An open and a second controlled study conducted by Mantovani et al. has suggested the possible therapeutic value of 1 Hz rTMS applied bilaterally to this site [17, 18]. The supplementary motor area is strongly

connected to the anterior cingulate, a cortical region that was previously reported to be closely associated with the pathophysiology of OCD [18]. However, one subsequent study combining both 1 Hz stimulation of the right DLPFC and 1 Hz stimulation of the supplementary motor area failed to find positive results [19].

10.3.1.1 Summary

Research has not supported the initial contention that DLPFC stimulation may have therapeutic benefits in OCD although high-frequency right-sided stimulation has not been systematically adequately evaluated despite initial promise. The supplementary motor area or orbital frontal cortex appears promising targets, but more detailed research is required to establish efficacy of stimulation at these sites.

10.3.2 Post-traumatic Stress Disorder

A series of relatively inconsistent studies have explored the potential application of rTMS in post-traumatic stress disorder (PTSD). The first of these explored the application of very low-frequency stimulation (0.3 Hz) applied to both the left and right motor cortex, producing a reduction in PTSD symptoms [20]. However, this was an uncontrolled study. Subsequently, studies have investigated a variety of stimulation paradigms including low- and high-frequency stimulation applied to the left DLPFC and low- and high-frequency stimulation applied to the right DLPFC [21–24]. Right-sided high-frequency stimulation has shown the greatest therapeutic promise in two studies which have evaluated stimulation to both hemispheres or compared different frequencies of stimulation applied to the right DLPFC [22, 23]. Given that neuroimaging-based models of PTSD have suggested that hypoactivity of the DLPFC is associated with hyperactivity of the amygdala and underlying illness symptoms and that right-sided changes are predominant in PTSD, a high-frequency approach to right-sided stimulation has some therapeutic rationale [25].

10.3.2.1 Summary

High-frequency stimulation applied to the right DLPFC appears to be the most promising rTMS approach to the treatment of PTSD but requires further evaluation.

10.3.3 Panic Disorder and Generalised Anxiety Disorder

Following several case reports, two randomised controlled trials have explored the use of rTMS in panic disorder, both investigating 1 Hz stimulation applied to the right DLPFC. In the first study, no significant difference was seen between active and sham stimulation in 15 medication-resistant patients [26]. The second study, in a slightly larger sample size ($n=25$), did find significant differences in response between active and sham stimulation [27].

Only one study has explored the possible use of rTMS in generalised anxiety disorder (GAD). This was an open-label study where 1 Hz stimulation was applied to the right DLPFC with the site determined by an fMRI activation scan [28]. Six out of ten patients met remission criteria for reduction in anxiety symptoms within this study.

10.3.3.1 Summary

Only limited research has explored the application of rTMS in panic disorder and GAD. There appears to be a possibility of therapeutic value of 1 Hz stimulation applied to the right DLPFC, but at this stage this has very limited empirical support.

10.4 Schizophrenia

Despite some advances in pharmacotherapy over the last 20 years, a significant percentage of patients with schizophrenia experience disabling refractory symptoms. Furthermore, side effects are common with current pharmacotherapy for schizophrenia resulting in high rates of early treatment discontinuation [29]. Thus, researchers and clinicians have sought novel treatments to target refractory symptoms. rTMS has been relatively extensively investigated as a treatment for schizophrenia vis-a-vis positive (e.g. hallucinations and delusions) and negative symptoms of schizophrenia, as well as cognitive dysfunction.

Increasingly schizophrenia researchers consider this disorder to be highly heterogeneous. Therefore, it follows that specific treatment of individual subcomponents of the syndrome, such as the negative symptoms or hallucinations, may yield greater success than non-specific treatments applied to all patients. It is unlikely that a brain stimulation technique that targets one brain region would be likely to improve multiple dimensions of the illness but may have specific value in ameliorating particular symptoms.

In this regard, rTMS protocols for treatment-resistant schizophrenia have targeted two main cortical areas with differing aims. Dysfunction in the prefrontal cortex is thought to underlie some of the positive and negative symptoms in schizophrenia. Initial treatment protocols targeting the DLPFC in schizophrenia were inspired by treatment protocols used for major depression. Analogous to the situation in depression, hypoactivation in prefrontal regions is thought to correlate with negative symptoms [30]. Thus, it was hypothesised that high-frequency rTMS applied to the DLPFC may improve negative symptoms by increasing cortical activity [31]. The other main cortical region targeted in rTMS studies has been the temporoparietal cortex (TPC). Although there are some contradictory findings, a number of studies have suggested that the pathophysiology of auditory hallucinations is related to hyperactivity in the left TPC [32, 33]. Based on this understanding, Hoffman et al. developed a low-frequency rTMS protocol applied to the left TPC to modulate the overactive state underpinning auditory hallucinations [34, 35].

10.4.1 Prefrontal Stimulation in Schizophrenia

Early rTMS studies in schizophrenia targeted the DLPFC as a non-specific treatment. The first published study used only 30 single rTMS pulses applied openly in a single treatment session and described some short-lived therapeutic effects [36]. In a second small open study, a statistically significant decrease in Brief Psychiatric Rating Scale (BPRS) scores was observed after ten sessions of 1 Hz stimulations applied to the right DLPFC [37]. The improvement was primarily seen in non-specific symptoms, such as anxiety and tension, rather than in the core symptoms of schizophrenia. A larger, controlled study with similar stimulation parameters failed to confirm any significant improvement in schizophrenia symptoms when rTMS was compared to a sham control [38].

High-frequency stimulation to the DLPFC as a treatment for positive symptoms was first studied in a small crossover design comparing left-sided active versus sham stimulation [39]. A significant reduction in BPRS scores was seen with active but not sham stimulation. However, three other studies of high-frequency stimulation of the left DLPFC have failed to demonstrate an improvement in positive symptoms [40–42]. A recent meta-analysis concluded that high-frequency stimulation of the DLPFC has failed to show improvement in positive symptoms as assessed by the positive and negative symptom scale-positive symptom score (PANSS-P) or the scale for the assessment of positive symptoms (SAPS) [43].

In contrast to the negative results found when targeting positive symptoms with high-frequency rTMS to the DLPFC, the treatment of negative symptoms with this approach has yielded somewhat more encouraging results. There have been a series of small parallel design trials. In several studies, there were no differences between active and sham groups [40, 44, 45]. However, four studies have shown a significant advantage of active over sham stimulation [42, 46–48]. Three of these studies [42, 46, 47] used higher stimulation intensity (>100 % of the standard resting motor threshold) and one of the studies used a longer treatment duration (15 days) than the negative studies (10 days) [46]. One of these two positive studies also carefully controlled for the possible confound of improved depressive symptoms using scores on the Calgary Depression Scale for Schizophrenia as a covariate: improved depression did not account for the observed improvement in negative symptoms [42]. Another study compared 20 Hz stimulation to stimulation provided at the patient's individual α-frequency with a sham condition [49]. α-Frequency stimulation was calculated as the patient's peak α-frequency from five frontal EEG leads. The rationale for enhancing activation by using the patient's own α-frequency was based on the hypothesis that a deficiency in oscillation at this frequency is related to the underlying pathophysiology of negative symptoms. Stimulation at the patient's α-frequency resulted in a significantly greater reduction in negative symptoms than the other three conditions. Two studies investigating the use of bilateral high-frequency stimulation have both reported no improvement in negative symptoms [50, 51].

Overall, the studies targeting refractory negative symptoms that used high-frequency stimulation targeted to the DLPFC have produced mixed results. The outcome of the studies may have been hindered by the short duration of treatment typically applied and low doses of rTMS used.

Until recently, no studies have specifically investigated the effect of rTMS applied to the DLPFC on cognition in patients with schizophrenia. Impaired cognition has been increasingly recognised as a primary deficit in schizophrenia [52]. Recent data suggests that high-frequency rTMS applied to DLPFC can improve performance on higher-order cognitive functions and selectively modulate γ-oscillations in frontal regions [53]. Given the prominence of cognitive deficits in patients with schizophrenia and the potential relationship of aspects of cognition such as working memory to high-frequency EEG oscillations, it seems worthwhile to investigate the effect of high-frequency rTMS of the DLFPC on cognition. Recently Barr et al. reported that bilateral rTMS applied at 20 Hz and targeted to the DLPFC could improve working memory deficits in schizophrenia in a study including 27 patients [54]. Working memory was assessed using the N-back task. rTMS significantly improved 3-back accuracy to targets compared to sham. There was also a trend towards significance for the effects of rTMS on the 1- versus 3-back suggesting that rTMS was more effective on working memory performance as difficulty increased. This small study suggests that rTMS should be investigated further as a possible treatment option for cognitive symptoms in schizophrenia.

10.4.2 Temporoparietal Cortex rTMS and Auditory Hallucinations

The most extensively investigated application for rTMS in schizophrenia has been the use of low-frequency stimulation applied to the left TPC (see Fig. 10.1), in an effort to ameliorate auditory hallucinations (AH). Initial studies were of a relatively short duration, but they still demonstrated a decrease in the frequency and intensity of AH [34, 35]. A larger, controlled study of 9 days of low-frequency left-sided (LFL) stimulation of the TPC found a substantial and significant reduction in AH compared to sham. Furthermore, this improvement was sustained in more than half of the improved subjects at 15 weeks posttreatment [55]. In an even larger controlled study, the efficacy finding was confirmed and the treatment demonstrated an excellent safety and tolerability profile (a consistent finding across subsequent studies) [56].

Several investigators have attempted to replicate and extend these findings using open, crossover and parallel randomised controlled designs with mixed results [57–68]. Of note, however, is an open study that correlated response to treatment with reduction in cortical metabolism (as measured by PET imaging) beneath the site of stimulation, substantiating the theoretical rationale for this treatment [65]. The mixed results likely relate to heterogeneity in the duration and intensity of treatment. Interestingly, two of the randomised controlled studies have found significant reduction in frequency and intensity of AH with less than 10 days of treatment [57, 58].

An initial meta-analysis of all acute rTMS treatment studies of AH found an effect size of 0.76 (95 % CI = 0.36–1.17) for LFL rTMS applied to the left TPC, despite variation in the duration and methods of stimulation [69]. Two recent meta-analyses confirmed the finding of a medium to large effect size [43, 70]. The authors point out that there is a large degree of heterogeneity in these studies. Heterogeneity issues included: protocol duration and intensity, differing placebo controls, lack of

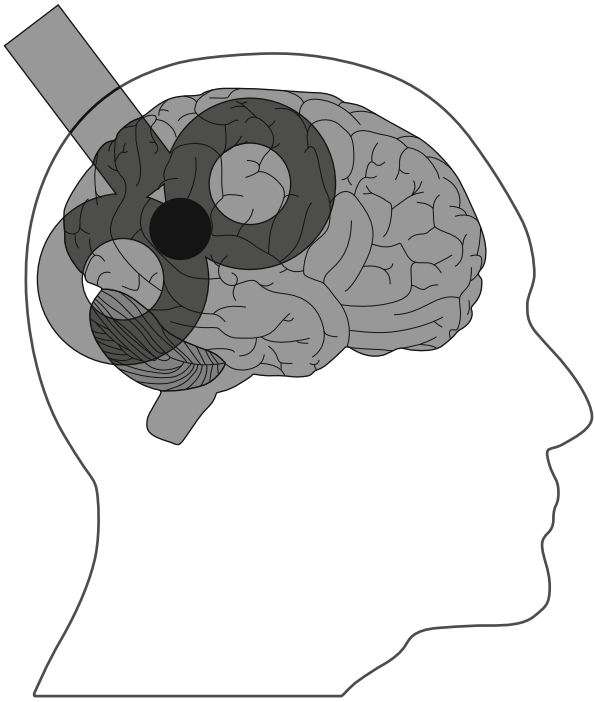

Fig. 10.1 The localization of the TMS coil over temporoparietal junction

adequate control of medications and inadequate assessment of treatment resistance. Furthermore, these authors comment about the need for better follow-up and the need for studies of maintenance treatment in patients that respond to an acute course of rTMS.

In an attempt to optimise efficacy, investigators have started to explore bilateral and right-sided TPC stimulation. Another approach taken to optimising efficacy has been the utilisation of MRI and fMRI to more specifically target the neuroanatomical structures involved in auditory hallucinations. The first study found no specific benefit of rTMS or of MRI-based localization [71]. A second study found an overall benefit with rTMS, but again no improvement with fMRI-based localization [72]. In another study, LFL rTMS was applied to a series of sites activated on fMRI scan for eight intermittent hallucinators or to a series of sites functionally coupled to Wernicke's area in eight patients with continual hallucinations [73]. Stimulation at the left TPC site resulted in a greater rate of reduction in auditory hallucination severity compared to stimulation at other sites. A novel imaging and treatment protocol in a case report has recently been published [74]. The investigators identified the area of highest activation during a language task using fMRI. The area correlated with the left superior temporal gyrus. They theorised that high-frequency stimulation (20 Hz) may reduce AH based on work showing disruption in higher cognitive functions such as speech production [75]. A follow-up study with rTMS targeted to the site identified on individual fMRI scans, in a group of 11 patients,

demonstrated decreased global severity and frequency of AH in 8 of 11 patients, with a large effect size after only 2 days (2,600 pulses) of treatment [76]. This is a striking finding that warrants further investigation with a randomised controlled study. The improvement was present 10 days after treatment in the whole sample and sustained for a mean of approximately 2 months. However, the cost of fMRI localization may be prohibitive for application to the wider population of patients experiencing refractory AH. Therefore, refinements in defining an optimal TPC site that can be found by approximation are necessary.

Beyond some follow-up data provided in a minority of studies, there is minimal data on the longer-term implications of treating AH with rTMS [56]. Fitzgerald et al. reported the successful retreatment of two patients who had relapsed following successful rTMS treatment, one of them on two occasions [77]. There is a report of maintenance rTMS in a patient for 6 months with some decrease in severity but no delay in relapse [78] and a second case where maintenance treatment was successful over an 8-month period [79]. One further case report described a patient who experienced improvement in AH after 1 week of treatment (twice daily low-frequency stimulation to the left TPC) and also in the second occasion following relapse 6 months later. After the relapse, the patient had sustained improvement over 1 year with once monthly treatment [80].We have treated a number of patients with repeated courses of rTMS for relapse of hallucinations and achieved consistent responses over time. We have also successfully utilised a clustered maintenance schedule (5 treatment sessions over 3 days every 4 weeks) in a small sample of patients with particularly difficult to treat symptoms and frequent relapse.

10.4.3 Summary

Evidence currently does not support the clinical use of rTMS in the treatment of negative symptoms or cognitive dysfunction in patients with schizophrenia. However, studies using longer-term and high-dose treatment are required to establish whether rTMS is effective for negative symptoms. Treatment of cognitive dysfunction with rTMS is a promising but new area of research. A more substantial research base has indicated that low-frequency rTMS applied to the left temporoparietal cortex appears to have some therapeutic benefits in ameliorating auditory hallucinations. Given the often disabling nature of these symptoms, clinical use of this technique could be justified in certain cases although overall response rates are not likely to be high.

10.5 Pain

Due to the long-standing and often disabling nature of chronic pain, rTMS and other novel approaches using brain stimulation techniques have been investigated over a number of years.

Approaches to the treatment of chronic pain with rTMS have focused on several different cortical sites. The main site for investigation, however, has been the primary motor cortex. Studies since 2001 have utilised high-frequency stimulation

applied to the motor cortex to try to transiently or persistently ameliorate chronic pain. In the first study of this sort, investigators applied 10 Hz stimulation to the primary motor cortex of patients with intractable neurogenic pain. Pain relief was achieved with a single session of stimulation, but this was short lasting and of modest effect [81]. A similar effect was seen in a second study investigating 10 Hz stimulation applied in patients with unilateral complex regional pain syndrome type I of the hand [82]. Subsequent studies have explored longer periods of stimulation. For example, Picarelli et al. randomised 23 patients with complex regional pain syndrome type 1 in the upper limb to commence standardised pharmacological treatment and either active or sham rTMS delivered in ten sessions at 10 Hz to the motor cortex contralateral to the affected side [83]. It was found that rTMS reduced pain intensities, particularly with ten treatment sessions, in a manner that was related to positive affective aspects of pain.

However, the analgesic effects of rTMS have not been consistent across studies with a number of negative studies reported (see review in [84]). Low-frequency rTMS appears to be less effective than high-frequency [85] and response appears to be dependent on the type of pain syndrome with facial pain, especially trigeminal neuralgia, appearing to respond better than other types of pain syndromes [84]. A recent Cochrane review, including 19 rTMS studies, concluded that there was evidence for short-term analgesic effects of single rTMS sessions, but limited evidence at this stage of longer-term treatment benefit [85].

A second site for potential treatment of chronic pain with rTMS is the dorsolateral prefrontal cortex (DLPFC) due to its role in top-down modulation of pain. Tolerability of experimentally induced pain has been shown to be modulated both by high-frequency stimulation of the left DLPFC [86] and low-frequency stimulation of the right DLPFC [87], both antidepressant rTMS paradigms. Early studies have begun to explore the potential of this form of stimulation in patients with chronic pain. For example, Borckardt et al. found analgesic effects of high-frequency left DLPFC stimulation in a small group of patients with neuropathic pain [88]. In contrast, 1 Hz stimulation applied to the right DLPFC may produce benefit in patients with pain related to fibromyalgia [89]. Notably, both of these approaches appeared to produce therapeutic effects that persisted over time and interestingly unilateral stimulation was able to achieve bilateral effects, something not seen with primary motor cortical stimulation. These characteristics make the potential applicability of prefrontal rTMS potentially greater than that of motor cortical stimulation. Interestingly, we have occasionally seen a reduction in chronic pain in patients receiving prefrontal rTMS treatment for depression with improvement in pain not necessarily correlated with improvement in depression severity

10.5.1 Summary

Promising initial research suggests that rTMS may be able to modulate chronic pain. Prefrontal stimulation appears to have considerable potential for clinical applicability but requires ongoing research.

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