

IS THERE POTENTIAL FOR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) AS A TREATMENT OF OCD?

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SUMMARY

Obsessive-Compulsive Disorder (OCD) is a common and highly debilitating psychiatric disorder. Amongst OCD sufferers are a significant number (40-60%) of so-called non-responders who do not fully respond to commonly available treatments, which include medications (Selective Serotonin Reuptake Inhibitors-SSRIs) and cognitive behavior therapy (CBT). Modern 'neuromodulatory' techniques such as Deep Brain Stimulation (DBS), repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) potentially offer alternative forms of treatment for OCD patients who either do not respond to, or are unable or unwilling to take SSRIs and undergo CBT. Although shown to be effective in treatment resistant OCD, DBS requires invasive neurosurgical procedures with associated risks. On the other hand, rTMS and tDCS are non-invasive forms of treatment, which are largely risk free, but the evidence of their efficacy so far is somewhat limited, with only small number of published studies. In this brief survey we will address the potential of rTMS as a therapeutic tool for OCD and review the published literature on the cortical targets for rTMS used so far. We will also discuss some of the newer variants of rTMS techniques only a few of which have been employed so far, and speculate whether there might be a place for rTMS as a standard treatment in OCD, along side CBT, SSRIs and DBS.

Key words: neuropsychiatric disorders - OCD - TMS - rTMS - neuromodulation

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Introduction

Obsessive-Compulsive Disorder (OCD) is a common and highly debilitating psychiatric disorder with a lifetime prevalence of 2.5% (Karno et al 1988). Though this is more than the double of the prevalence of schizophrenia, OCD often does not get the same attention and indeed is under-diagnosed as many 'suffer in silence' and do not seek help often due to embarrassing symptoms, despite having fairly good insight into their conditions.

OCD has been ranked the tenth most disabling illness, in terms of lost earnings and diminished quality of life by the World Health Organisation (WHO). Like many psychiatric disorders, it not only causes significant burden to the individual, but also to the family, health services, and the society as a whole. Individuals with OCD, at times "self medicate" with drugs and or alcohol to cope with their symptoms, leading to the development of drugs and alcohol related comorbid disorders (Torres et al 2000). OCD results in large economic burden with one report estimating the cost of over \$8 billion to United States annually (DuPont et al 1995). In addition to substance misuse disorders, lifetime comorbidity with depression and other anxiety disorders is also common (Pigott et al 1994).

OCD presents clinically with obsessions, which can be described as egodystonic, unwanted thoughts, images, or impulses that repeatedly enter sufferer's mind causing anxiety. Whilst, compulsions consist of repetitive, time-consuming behaviors (examples of which

include repetitive cleaning and checking) or mental acts, which are often performed to neutralize the anxiety provoked by obsessions (Heyman et al 2006). Most OCD sufferers present with mixture of obsessional thoughts and compulsive acts, however, some show predominance of obsessional thoughts or ruminations, whilst others may present with largely compulsive acts.

Use of Selective Serotonin Reuptake Inhibitors (SSRIs), especially when combined with cognitive behaviour therapy (CBT) has clearly improved the management of OCD (Skapinakis et al 2016). However, unfortunately, it is estimated that a significant percentage (40-60%) of OCD patients do not fully respond to SSRIs (Kaplan & Hollander 2003). Indeed some OCD patients do not tolerate SSRIs, whilst others are unable or unwilling to utilize CBT, thus leaving a significant number of OCD sufferers in search of alternative forms of treatment, which do not involve conventional pharmacotherapy (SSRIs) or psychological treatments such as CBT. Furthermore, unlike for treatment of resistant depression, electroconvulsive therapy (ECT) has generally not been found to be useful in the management of treatment-resistant OCD.

The relatively new electrophysiological or neuromodulatory techniques such as Deep Brain Stimulation (DBS), transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) offer alternative forms of treatment for OCD. In this paper, we will explore the possible role of rTMS as an alternative treatment for OCD.

Transcranial Magnetic Stimulation (TMS) & Repetitive TMS (rTMS)

First introduced in Sheffield, England by Anthony Barker and colleagues (Barker et al 1985), Transcranial Magnetic Stimulation (TMS) was soon taken up by neurophysiologists, neurologists and psychiatrists, initially as an investigative tool and subsequently, with modifications, as a therapeutic tool for neuropsychiatric disorders, the list of which continues to expand.

TMS involves placing a wired coil over the scalp and generating an electric current pulse, which in turn produces a time varying magnetic field that passes through the skull painlessly and induces electric current, thus depolarizing cortical neurons. The location of the coil on the scalp is determined by the choice of which underlying cortical region should receive stimulation. These effects of stimulation can progress further to the deeper sub-cortical neural circuits through trans-synaptic mechanisms (Hallett 2000).

The subsequent effects of TMS/rTMS through the brain depend upon a number of extrinsic and intrinsic factors. The former include, motor threshold (MT), frequency of stimulation (measured in Hz), number of stimuli and the time period over which the stimulation is carried out. The intrinsic factors include, anatomical and functional connections in the brain.

Many studies, including those employing neuroimaging, have provided evidence for the effects of rTMS on the brain. It has been noted that, in general low frequencies (1-5 Hz) lead to decrease in neuronal excitability and cerebral blood flow, whilst higher frequencies (≥ 5 Hz) increase neuronal excitability as well as cerebral blood flow (Speer et al 2000). By convention, single pulse stimulation is described as TMS, whereas repeated pulses with a frequency of stimulation of 1Hz or above is described as repetitive Transcranial Magnetic Stimulation (rTMS). TMS machines can produce stimulation frequencies of up to 50 Hz.

Single pulse TMS is capable of producing, for example, a brief movement of upper limb when the corresponding motor cortical region is stimulated. Single pulse and paired pulse TMS have become useful tools for exploring, the pathophysiology of neurological and psychiatric disorders. Given that the effects of single pulse TMS are short-lived, it is necessary to use rTMS for the production of sustained, long lasting effects, which is what is required when exploring for its therapeutic potential in neurological and neuropsychiatric disorders (George et al 1995).

rTMS is well-tolerated, though some patients have complained of minor headaches, and seizure remains a potential risk. However, in practice, seizures have been very rare, particularly when the safety protocols are followed (Wasserman et al 1998).

rTMS has clear advantages over ECT. It is non-invasive, requires no anesthesia and overall relatively inexpensive. Additionally, it is relatively user-friendly and, most importantly free of the unfortunate stigma attached to ECT.

rTMS has been approved by both FDA (USA) and NICE (UK) for the treatment of depression. However, currently the use of rTMS for treatment of OCD largely remains laboratory based, though there are private TMS clinics around the world, claiming to offer rTMS treatment for OCD.

Pathogenesis of OCD and potential targets for rTMS

Historically thought of as a psychogenic disorder, OCD is now well established of as a neuropsychiatric disorder thanks to numerous studies utilising many different techniques (lesion studies, neuroimaging), which have pointed to Cortico-Striato-Thalamo-Cortical (CSTC) circuit abnormalities in the brain. In particular, abnormalities in one fronto-striatal circuit including the orbitofrontal cortex (OFC), anterior cingulate cortex and basal ganglia has been highlighted. (see review by Chamberlain et al 2005; Fettes et al 2017).

Deeper brain areas, including the anterior limb of the internal capsule, the nucleus accumbens (ventral striatum) and the subthalamic nucleus (STN) have been targeted by Deep Brain Stimulation (DBS) with remarkable success in improving treatment resistant OCD symptoms (Kohl et al 2014). However, given the invasive nature of DBS and the risks associated with the neurosurgical procedure, it is not surprising that this successful therapeutic technique is reserved for the very severe treatment resistant cases of OCD.

Many studies have demonstrated dysfunction in several brain areas located more superficially and hence potential therapeutic targets for repetitive Transcranial Magnetic Stimulation (rTMS). These areas include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortices (mPFC), anterior cingulate gyrus, and supplementary motor area (SMA) (Del Casale et al 2011, Fineberg et al 2011) all of which have been implicated in OCD by various authors (Chamberlain et al 2005, Fettes et al 2017).

Cortical targets for repetitive Transcranial Magnetic Stimulation (rTMS) in treatment of OCD

Dorsolateral Prefrontal cortex (DLPFC)

Hot on the heels of early therapeutic studies of rTMS in depression (George et al 1995, Pascual-Leone 1996), came one of the first rTMS studies in OCD by Greenberg and colleagues. Hypothesizing that inhibiting prefrontal cortical activity would improve OCD symptoms, they randomized 12 patients and stimulated the left dorsolateral prefrontal cortex (DLPFC), right DLPFC, and for the control group, a mid-occipital site with rTMS parameters of 20 Hz, 2 second/minutes for 20 min, at 80 % of the motor threshold (MT). They found reductions in patient-rated compulsions (but not obsession) over 8 hours with active stimulation of the right DLPFC (Greenberg et al 1997).

Over a number of years, other researchers followed Greenberg and colleagues in targeting the DLPFC on OCD, however, some conflicting findings resulted. Thus, Alonso et al (2001) failed to show significant improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS, Goodman et al 1989) between sham and an active stimulation group in 18 patients. Utilizing double-blind, placebo-controlled conditions, they stimulated the right DLPFC using 1Hz rTMS at MT of 110% (for active rTMS) and MT of 20% (for sham rTMS) for 20 minutes over 18 sessions.

During the same year, an open rTMS study (10Hz, 100% MT, for 10 sessions of 2.5 minutes) of 12 patients with OCD was published by Sachdev et al (2001). This showed a reduction in Y-BOCS scores (57% for stimulation of right DLPFC and 27% for left DLPFC). However, after correcting for depression the significance of this reduction in Y-BOCS was lost. Sachdev et al (2007) also failed to show beneficial effects of rTMS for OCD in a double-blind placebo-controlled study of stimulation of left DLPFC (10Hz, 110% MT, 10 sessions). Further studies utilizing the stimulation of either the right or left DLPFC (between 1-10Hz) also failed to show significant difference between active and sham groups (Prasko et al 2006, Sarkhel et al 2010, Mansur et al 2011). Despite, these generally negative results, a relatively recent Chinese study reported positive results (significant reduction in Y-BOCS-obsessions) with bilateral stimulation of DLPFC in OCD patients (46 OCD patients, 25 receiving active and 21 sham stimulation). These researchers used novel technique of alpha electroencephalogram-guided (α EEG) TMS to determine each patient's TMS motor threshold thus allowing for individual titration of 10 sessions of rTMS treatment given over two weeks (Xiaoyan et al 2014). Again contrarily to earlier studies, further support for the benefits of 1 Hz rTMS for right DLPFC stimulation has also come from very recent study conducted in Egypt (Elbeh et al 2016). Overall, twenty years after Greenberg's original observations, there is still no consensus on the efficacy of rTMS of the dorsolateral PFC for OCD.

Pre-Supplementary Motor Area (pre-SMA), Supplementary Motor Area (SMA) and Orbitofrontal Cortex (OFC)

Given that DLPFC stimulation had produced largely negative results, researchers turned to other cortical region, such as pre-supplementary motor area (pre-SMA), supplementary motor area (SMA) and orbitofrontal cortex (OFC) as possible stimulation sites. The rationale behind use of these sites was based upon the increased understanding of neural circuits involved in pathophysiology of OCD (See Fettes et al 2017).

The SMA is linked to motor planning and response-inhibition and connects to regions involved in emotional and cognitive processes (Mostofsky et al 2008, Picard et al 2003, Oliveri et al 2003). Support for the use of the pre-SMA site came from cortical excitability studies in

which inhibition of primary motor cortex (measured by resting motor threshold (RMT) and short interval cortical inhibition (SICI)) was found to increase when 1Hz rTMS was applied to the pre-SMA. In addition, inter-hemispheric asymmetry normalises with rTMS treatment and correlates with clinical improvement in OCD (Montovani et al 2013, Montovani et al 2007).

Though limited by an open design and small sample, Montovani and colleagues demonstrated sustained clinical improvement in 60% of the patients (improvement in Y-BOCS and Yale Global Tic Severity Scale (Y-GTSS)) by targeting the SMA. In this study, 10 patients (5 with OCD, 3 with Tourette's syndrome and 2 with both) were recruited and stimulated over SMA bilaterally with rTMS parameters of 1 Hz, 100% MT, 1200 stimuli/day over 2 weeks (Montovani et al 2006). They followed up this study with a randomized sham-controlled bilateral stimulation of SMA in 21 medication resistant patients with OCD. Using rTMS parameters of 1 Hz, 100% MT, and 1200 stimuli/day over 4 weeks, they found that the active stimulation group exhibited a 25% reduction in Y-BOCS compared with 12% for the sham group, along with response rate of 67% for active and 22% for sham rTMS (Montovani et al 2010).

A study by Kang and colleagues investigating effects of sequentially combining rTMS (1 Hz, 110% MT, lasting 20 minutes, totalling 10 sessions) to right DLPFC and the pre-SMA reported no significant difference between active and sham groups at the end of treatment (Kang et al 2009). However, for this study it has been argued that its lack of efficacy could be explained by the sham treatment not being satisfactory due to the angle (45°) at which the coil was positioned against the scalp, possibly causing partial magnetic stimulation.

By contrast, a sham-controlled study targeting pre-SMA bilaterally (22 OCD patients, 12 active, 10 sham, 1 Hz, 100% MT stimulation, 10 sessions) by Gomes and colleagues did show significant improvement in Y-BOCS scores with 35% reduction in active compared with 6.2% reduction in sham group at 14 weeks (Gomes et al 2012). Further support for the utility of bilateral rTMS stimulation of SMA (1 Hz, 100% MT, 1200 stim/day, for 4 weeks) came from Montovani and colleagues' demonstration of an average reduction in Y-BOCS score of 25% in the active group compared with 12% in the sham controls (Montovani et al. 2013). Recently, Pelissolo and colleagues reported in 40 medication resistant OCD patients over 4 weeks, the effectiveness of rTMS (1 Hz, 100% RMT, 26 minutes sessions (total of 1500 pulses/day)) in targeting pre-SMA. They used neuronavigation to localise pre-SMA, hence arguing that localisation was more precise. The researchers explained their negative results as possibly due to the highly refractory nature of their patient group (Pelissolo et al 2016).

Following Pelissolo et al's negative study, there have been two very recent studies reporting positive outcomes of rTMS targeting the SMA. Pallanti and colleagues described a study where they compared 25

SSRIs-refractory OCD patients, treated with 3 weeks of 1 Hz, bilateral rTMS over the SMA, with 25 SSRIs-refractory OCD patients treated with antipsychotics. They found positive response with 1 Hz rTMS over SMA amongst 2/3 of SSRIs-refractory OCD patients compared with only 1/4 responding to antipsychotics, thus importantly suggesting the superiority of rTMS targeting SMA over the treatment with antipsychotics in OCD patients (Pallanti et al 2016). At the time of writing and in advance of the publication of their full paper, Lee and colleagues from South Korea have provided further support for this conclusion and suggested that 1 Hz rTMS over SMA could be an efficient and safe augmentation strategy for treatment-resistant OCD patients. In an open label study, they reported significant reduction in Y-BOCS (mainly compulsions) score at the 4th week of treatment with 1 Hz rTMS over the SMA in patients with treatment-resistant OCD (Lee et al 2017).

Despite the evidence showing functional hyperactivity in the orbitofrontal cortex (OFC) in OCD and its implication in the development and pathophysiology of compulsive-like behaviour, (Alpetkin et al. 2001; Evans et al. 2004), this region has attracted less attention and to our knowledge, there have only been 2 published rTMS treatment studies. This may be due to practical problems in stimulating the OFC with rTMS, such as access, the OFC is rather deeply buried beneath the scalp, and side-effects (e.g. excessive twitching of eye muscles).

Ruffini and colleagues carried out the first exploratory rTMS treatment study of OFC. In their study, 23 treatment resistant OCD patients received rTMS (6 active and 7 sham) with low frequency of 1Hz, at 80% MT over the left OFC, 10 minutes daily for 15 days (over 3 weeks). They found a significant reduction in Y-BOCS scores for active compared with sham stimulation for 10 weeks after the end of rTMS, however, this significance was lost after 12 weeks, suggesting only a time-limited improvement (Ruffini et al 2009).

In the second published rTMS stimulation of the OFC in OCD, Nauczyciel and colleagues targeted the right OFC. They used double-cone coil, which is said to allow deeper stimulation compared to figure-of eight coil (Deng et al 2013). In this randomised, double-blind, crossover design study, they carried out two, 1-week stimulations (active and sham), which were separated by 1-month washout period. They stimulated the right OFC using following rTMS parameters: 1 Hz, 120% MT, twice daily (1200 pulses/session). A subgroup of 10 patients underwent two PET scans to determine direct effects of rTMS and to confirm the hypothesis that the beneficial effects of rTMS were related to a decrease in OFC metabolism. This study took 3 years (2009-2012) to complete and recruited 22 OCD medications treated patients, although only 19 were included. The results showed significant decrease in Y-BOCS scores for both active and sham stimulation, though the decrease was larger for active stimulation. However, no difference was found a month after the second period of stimulation. The PET scan results showed decreases in

metabolism of the bilateral orbitofrontal lobes, the decrease being more extensive on the right side. The decrease in Y-BOCS scores correlated with the decrease in metabolic activity of the right OFC. The authors argued for the potential benefits (investigative and therapeutic) of carrying out larger studies of stimulation of OFC with rTMS in OCD. Nevertheless, they accepted that at the time, the therapeutic role of rTMS in OCD through stimulation of the OFC was somewhat limited (Nauczyciel et al 2014).

CONCLUSION

The future of rTMS treatment in OCD

Despite the passage of 20 years since the publication of the first paper on the effects of rTMS in OCD (Greenberg et al 2007), the investigative and therapeutic research using rTMS in OCD lags far behind that in depression.

Following on the heels of depression research, the early researchers targeted either right or left DLPFC with mostly disappointing results. Yet a recent study utilizing a different method called alpha electroencephalogram-guided (α EEG) TMS has shown some promise and is clearly worth exploring further (Xiaoan et al 2014). Moreover, another recent study has produced positive results for stimulation of the right DLPFC (Elbeh et al 2016). Hence, despite earlier disappointing results, the stimulation of DLPFC may still hold some promise.

Contrary to the inconsistent results obtained from the stimulation of the DLPFC, the targeting of pre-SMA and SMA with rTMS has produced number of positive results.

As for the stimulation of the OFC, to our knowledge, there have only been 2 published studies that have shown improvement in OCD symptom, however, this improvement was time limited.

A recent meta-analysis on the short-term therapeutic effects rTMS in OCD has suggested superiority of active stimulation targeting DLPFC (right, left and bilateral) as well as SMA, however, it excluded studies targeting OFC (Zhou et al 2017).

Despite these positive findings of the meta-analysis performed by Zhou and colleagues, detailed examination of the limited number of studies in past 20 years in fact points towards a somewhat mixed picture, suggesting that much more work is still needed and that we are still quite far from drawing definitive conclusions with regards to the therapeutic role of rTMS in OCD.

The lack of standardisation of rTMS parameters (precise targets, type of coils, frequency, intensity/motor threshold, number of stimuli in each sessions, number of sessions and the period over which the treatment is given) and of OCD patients (severity of illness, type of medications, lack of precise definition of treatment resistance) in these studies makes comparisons somewhat difficult.

In addition, the issue of responders and non-responders for any form of treatment is important.

Research suggests that sleep disorders are prevalent amongst OCD sufferers (Diaz-Roman et al 2015). A recent study has shown that for OCD sufferers, sleep disorders are far more frequent amongst the non-responders of rTMS treatment compared with those who are found to be rTMS responders (Donse et al 2017). Clearly this is an important factor, which should be taken in to consideration when selecting OCD patients for rTMS therapeutic studies.

New Developments

In the last few years there have been some new developments with regards to the types of rTMS methods being utilised: Wu and colleagues have published a case report of the utility of continuous Theta-Burst rTMS stimulation (cTBS) over the right DLPFC, which showed improvement in Y-BOCS score (19 to 8) in OCD patient. They also performed functional MRI, which showed substantial reduction in provoked symptoms related BOLD activity in the right DLPFC following cTBS (Wu et al. 2010). TBS refers to an rTMS protocol where pulses are applied in bursts of three, delivered at a frequency of 50 Hz and an inter-burst interval of 200 ms (5 Hz). There are two types of TBS, continuous (cTBS) and intermittent (iTBS). cTBS refers to bursts of 3 pulses at 50 Hz, applied at a frequency of 5 Hz for either 20 seconds (100 bursts) or 40 seconds (200 bursts). Whilst in iTBS, 20 2s periods (10 bursts) of TBS are applied at a rate of 0.1 Hz (Huang et al 2005). TBS has been successfully used in many depression treatment studies and has the advantage of needing much shorter time (as short as 7 minutes compared to 37 minutes in standard rTMS protocol) for treatment and is clearly worth exploring further in rTMS/OCD research (Berlim et al 2017). In addition to the TBS rTMS protocol, consideration could be given to use of combining accelerated form of rTMS with a TBS protocol shown to be effective in treating depression in 4 days (Duprat et al 2016).

Some researchers have advocated the use of so-called deep TMS (dTMS) that targets deeper neuronal structures to treat OCD patients. In a double-blind controlled study using dTMS or a sham coil, Carmi et al (2015) treated a group of 40 OCD patients (during symptom provocation) who were divided into two groups, receiving either 20 Hz or 1 Hz stimulation targeting the medial prefrontal and the anterior cingulate cortices. They showed significant improvement in Y-BOCS scores in the active 20 Hz group compared to the 1Hz and placebo groups (Carmi et al 2015). Further support for the use of dTMS (using double-cone coil) has come from Modirrousta and colleagues from their open label study in which they show improvement in OCD symptoms in 10 OCD patients who received 1Hz stimulation over the medial prefrontal cortex (mPFC) for the period of 10 days (Modirrousta et al 2015).

In addition to above, considerations could also be given to priming the cortical neurons with tDCS so that they are more responsive to rTMS (Siebner et al 2004), hence interestingly raising the possibility of combining two non-invasive neuromodulatory techniques.

In conclusion, published research so far points towards rTMS as potentially a valuable treatment tool for OCD. Large and better designed multicentre studies, with some standardisation of rTMS protocols and utilising some of the newer techniques, in combination with imaging tools will not only give a better understanding of the precise cortical targets for rTMS, but are also likely to address the question definitively, whether rTMS should be part of treatment protocol for OCD along with SSRIs and CBT. We believe the time is ripe to expand the research into the treatment of OCD with rTMS.

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Contribution of individual authors:

Rashid Zaman and Trevor W. Robbins jointly conceived the idea of the paper.

Rashid Zaman reviewed the literature and wrote the first draft.

Trevor W. Robbins revised the manuscript.

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