Indirect Priming rTMS for Treatment-Resistant Obsessive Compulsive Disorder: A Prospect that Demands Exploration

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Obsessive compulsive disorder (OCD) remains a challenging and debilitating disorder to tackle, even for experienced psychiatrists. Up to 40% of patients of OCD fail to respond satisfactorily to conventional treatment options and 10% remain totally resistant.[1] Novel treatment options are emerging, but OCD is still grueling for something more than the existing paraphernalia. Repetitive transcranial magnetic stimulation (rTMS) is one of such novel treatments being tried in OCD. Results from rTMS in OCD have been inconsistent, and even in cases with an initial response, relapses have been wearisome.[2] So, there is huge scope for improvement with regards to novel paradigms, one of which is priming rTMS. This is known to be effective and has lasting effects in cases of resistant verbal auditory hallucinations and resistant depression.[3]

Priming, in general, is an implicit memory effect in which exposure to one stimulus influences the response to another stimulus.[4] In rTMS, "priming" means pretreatment stimulation that involves a period of high-frequency stimulation at low intensity preceding the low-frequency stimulation, so as to enhance the neural response.[4] Brief pretreatment with stimulation in the theta range notably increases the ability of subsequent 1 Hz stimulation to produce a decrease in synaptic ability.[5] Moreover, it can be so brief or mild that it has no detectable effects of its own on synaptic transmission. This phenomenon, in which previous neuronal activity modulates the capacity for sequential plastic change, has been termed "metaplasticity," and this has previously been demonstrated in healthy volunteers.[5,6]

In cases of OCD, the recommended target site for rTMS is the supplementary motor area (SMA), which is the most anterior portion of area 6 of Brodmann on the medial surface of the frontal lobe. It is difficult to target, since it is located in interhemispheric fissure rather than being exposed on the lateral surface of the hemisphere.[7] Magnetic stimulation can be delivered through the coil positioned tangentially to the skull, with the handle parallel to the sagittal axis (pointing to the occipital area), with the center of the figure-8 coil over the site to be stimulated where the maximum field would be generated. With this orientation, current spread is greatest along the sagittal plane, and lateral current spread is minimized. This is the most effective orientation for stimulating SMA, given its midline structure and orientation.[7] Site of stimulation of SMA involves both right and left halves; priming it directly with high-frequency stimulation is a challenge in a patient who is on drug combination that can potentially decrease the seizure threshold, which is usually the case with patients of OCD. So, taking a cue from fMRI findings that show that rTMS protocols can evoke changes in neural activity and functional connectivity between remote brain regions,[8] and considering safety, we propose to prestimulate the left dorsolateral prefrontal cortex (DLPFC) as "indirect prestimulation" to achieve the priming effects, as it is also a part of cortico

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striato thalamocortical loop and has been a main target area for high frequency rTMS in depression and OCD as well.[9] These factors make left DLPFC a suitable site for indirectly priming the proposed target site of SMA in treatment-resistant OCD cases, as a proof of concept principle.

We present two cases who responded and maintained the response to indirect priming rTMS, opening a new avenue for research.

Case 1

A 22-year-old single female, who is a graduate, presented with four years' history of repetitive, intrusive thoughts of dirt and contamination, repetitive washing, intrusive thoughts of blasphemy, and ritualistic behavior. The illness was insidious in onset, was precipitated after a dog bite, had a continuous course, and was deteriorating with time. There was no significant past, family, or personal history, and her premorbid personality was well adjusted. She was an above-average student who had scored 90% in 12th board exams. However, her academic performance had deteriorated after the onset of the illness. She was on regular treatment for about 3.5 years, from two different psychiatrists at different periods. She received fluoxetine up to 120 mg/day, with clomipramine 225 mg/d, for six months, along with risperidone 1–3 mg/d and or aripiprazole 10–15 mg/d in between. There was history of receiving cognitive behavioral therapy (CBT) sessions from a clinical psychologist during the same time. At last, she had also received 15 sessions of conventional low-frequency rTMS over the SMA, which led to around 30% improvement in her Yale Brown Obsessive Compulsive Symptoms (Y-BOCS)[10] rating. However, there was relapse within two weeks of stopping the rTMS sessions.

On index presentation, she was already on fluvoxamine 400 mg/d and clomipramine 150 mg/d for the past eight months, with 30% subjective improvement, which was the best to date, and fluctuating symptom severity was a major concern. On mental status examination (MSE), she had an anxious affect, obsessive thoughts of contamination, obsession of blasphemy, compulsive washing and bathing, compulsive chanting, and counting rituals, with fair insight. Y-BOCS scale total score was 28/40.

Considering failed trials of two separate SSRIs along with CBT sessions and existing symptomatology, diagnosis of treatment resistant OCD, mixed obsessional thoughts and acts, was made and management plan was discussed with the patient and family.

There was further worsening of symptoms, with the Y-BOCS total score of 34/40 in next two weeks. Scores in Hamilton Depression Rating Scale (HAM-D)[11] and Hamilton Anxiety Rating Scale (HAM-A)[12] were 18 and 13, respectively, suggesting associated depressive and anxiety symptoms. Hence, it was planned to augment the well-tolerated regime of fluvoxamine and clomipramine with rTMS sessions. Conventional low frequency rTMS sessions over SMA were started. Five 30-minutes sessions were given in a week, with at least 24 hours' gap between two sessions, for three weeks. YBOCS score at the end of the sessions was 22/40. She was followed up after a month, wherein she showed deterioration, with Y-BOCS score rising to 28/40. As the improvement was not sustained over time, it was planned to implement indirect priming rTMS. The paradigm we followed included 10 minutes of high frequency 6 Hz rTMS as indirect priming, using figure-8 coil, with 20 trains of five seconds duration, total of 600 stimulations, over left DLPFC, at 80% resting motor threshold (RMT), followed by low-frequency 1 Hz rTMS for 20 minutes, 1200 continuous pulses over SMA, at 100% RMT. Pre-stimulation intensity was kept at 80% RMT, keeping the possibility of reduced seizure threshold. One session was of 30 minutes; five such sessions/week were given, each separated by at least 24 hours. A total of 10 sessions were given over two weeks.

The patient tolerated the sessions well, reporting no side effects. Dose of medications were kept constant throughout. She showed substantial improvement, with Y-BOCS score dropping to as low as 16/40, by the end of sessions in two weeks. HAM-D as well as HAM-A scores also came down to 7 each. Considering the plateaued-out response, we did not continue the sessions further. Patient was followed up and monitored fortnightly, due to a fear of relapse. The score on Y-BOCS was 18/40 when she came for follow-up visit after two weeks. However, there was no further change thereafter. Three months of regular monitoring showed stagnation of Y-BOCS score at 18/40, and also HAM-D, HAM-A scores below 7, with which the patient's academic performance improved and the distress decreased.

In the latest follow-up, one year after receiving indirect priming rTMS, the patient reported having cleared the graduate examination and was hopeful of going for higher education. On MSE, there was obsession of dirt and contamination, with decreased frequency and distress, along with compulsive washing lasing for around one hour/d. Blasphemous thoughts and rituals were no more troublesome.

Case 2

A 35-year-old married male, a shopkeeper, presented with eight years of illness characterized by thoughts of dirt and contamination and excessive washing behavior interfering with the day-to-day activities. His wife revealed on and off counting rituals when faced with stress. There was avoidance behavior wherein he begins closing his shop early, to avoid using public toilets, for fear of contamination. He had been pestering his wife to wash his clothes and shoes in a ritualistic manner, spending way more water, soap, and time than usual. MSE revealed obsessions of contamination, compulsive ritualistic washing, and proxy compulsions, with good insight.

The patient had been taking medications for more than five years, from different psychiatric centers. Treatment review revealed that patient has had adequate trials of fluoxetine up to 80 mg/day as well as sertraline up to 200 mg/d, 14 months and 4 months, respectively. There were other SSRIs, given for brief periods only, either due to poor tolerance or poor response. Considering the best response to date being with fluoxetine 80 mg/d, it was further augmented with clomipramine, which was hiked to 150 mg/d gradually along with exposure and response prevention therapy. The patient reported about 20% subjective

improvement after four weeks of optimizing the dose, that is, nearly six weeks from the initiation of clomipramine augmentation. His Y-BOCS score was 30/40. However, there wasn't much change in compulsive or avoidance behavior, which were causing distress to the family and financial losses.

Considering the treatment resistance, we planned to augment the medications with rTMS. Taking a cue from the previous case, keeping reduced seizure threshold in mind and to get a sustained response, indirect priming rTMS was planned and discussed with the patient and family. The same rTMS protocol was followed as with the previous case, that is, 10 minutes of 6 Hz rTMS as indirect priming over left DLPFC at 80% RMT, followed by 1 Hz rTMS for 20 minutes, over SMA at 100% RMT. Five such sessions were given per week, each separated by at least 24 hours. The patient began reporting improvement in symptoms by the first week itself. However, the sessions were continued for the next two weeks, as there was no plateauing of response by the end of 10 sessions. Y-BOCS score decreased over days, gradually reaching 16/40 by the end of 15 sessions. The dose of medications was kept constant throughout. The patient had reported tinnitus for a few minutes after the first session, which was relieved with reassurance. There was a slight increase in the Y-BOCS score in the next two weeks, to 20/40. However, his functioning improved and avoidance decreased. He was able to carry out his work on full-time basis, though he reported distress on using the public toilet. The patient was followed up for the next three months, and there has been no further change in his condition.

Discussion

The rationale for the initial use of rTMS in OCD was based on the functional neuroimaging findings that established abnormalities in the orbitofrontal-subcortical circuits, especially the orbital frontal gyri and medial caudate nuclei.[13] However, because of the variability of the stimulation site and different protocols that have been used for rTMS, it is difficult to draw absolute conclusions regarding the effect, though safety is well established.[14] Low-frequency rTMS applied over the SMA[15] or the left OFC[16] have been associated with significant improvements in OCD when compared to sham rTMS. A few other studies had shown positive effects after stimulation of the right and left prefrontal cortex as well as the SMA, with response rates ranging from 25% to 60% in patients of treatment-resistant OCD.[15] A recent study found that low-frequency rTMS over pre-SMA is not effective as an augmenting agent and suggested the need to explore alternate rTMS protocols in OCD.[17] Contrary to this, yet another study found anodal tDCS stimulation to be effective as an augmentation to SSRI-resistant OCD, suggesting SMA to be a potential target area for neuromodulation in OCD.[18] As of now, there is no consensus with respect to the target area, stimulation frequency, duration, or the number of sessions of rTMS in patients of OCD, though low frequency over the SMA is the preferred option by many.

Priming rTMS has been studied in a few neurological as well as psychiatric conditions like stroke, resistant auditory verbal hallucinations, and depression, giving consistent positive results.[3,19] Going with the same trend, prestimulation was found to be effective in our cases of resistant OCD, too, the effect of which persisted even long after the cessation of sessions. This also implies that priming in rTMS can be triggered at a related yet different target area, which is practicable and acceptable. In both cases, sessions were well tolerated with no serious adverse effects. It has implications especially in cases where there is a predisposition to seizures due to various reasons, including drug regimens that decrease the seizure threshold, as in our cases. Low-frequency rTMS over SMA is known to produce long-term depression (LTD), reducing the hyperexcitability in OCD. Upon this, priming is believed to have a metaplastic effect that can allow additional increments of LTD at a later stage.[20] That means the improvement that was observed at the end of the second/third week, respectively, should have continued with some intensity further, which did not take place in our cases, indicating some other mechanism underneath, which warrants randomized controlled trials on this paradigm and exploration of its biological underpinnings. Combined or additive effect of two stimulations, namely high-frequency but low-intensity stimulation at left DLPFC followed by low-frequency, full-intensity stimulation at SMA, is less likely, considering the shorter duration and lower intensity with which the former stimulation was given. However, functional imaging in these cases possibly could have yielded better insights into the underlying mechanisms, which is a potential avenue for future studies. It is worth exploring this paradigm in further controlled studies with adequate research design.

Declaration of Conflicting Interests

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