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TMS for OCD

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Abstract

Introduction: Obsessive compulsive disorder (OCD) is a common disabling condition, which greater than 40% of patients do not respond to the available treatment options. Imbalances in the cortical-striatal-thalamic-cortical circuits have proven to be useful psychosurgical treatment targets making this circuit disorder an optimal target for intervention with TMS.

Methods: PubMed and clinicaltrials.gov were reviewed for sham-controlled therapeutic rTMS studies for OCD.

Results: Eighteen relevant studies are presented in a narrative fashion along with relevant methodological details, and distinctions.

Conclusions: High and low frequency stimulation to lateral prefrontal cortices does not appear to have consistent efficacy in the small studies done to date. Several small studies with non-blinded operators suggest that low frequency high intensity rTMS to the supplementary motor area with a figure-8 coil reduces OCD symptoms. A fully blinded multicenter study is warranted to confirm this finding. A promising pilot study and a subsequent multicenter study of high frequency high intensity deep rTMS with the HAC/H7 coil to the bilateral prefrontal orbitofrontal and anterior cingulate cortices were completed with positive results. Many areas of uncertainty remain, such as the optimal state of the circuitry during stimulation and identifying a priori biomarkers for responders and non-responders to specific protocols.

Keywords: rTMS, dTMS, TMS, OCD, ACC, SMA, OFC, obsessive compulsive disorder

1. Introduction

The DSM 5 criteria for obsessive compulsive disorder (OCD) are specific. Patients can have either obsessions, compulsions or both. Obsessions are defined as unwanted thoughts, images or urges. Compulsions are repetitive behaviors or mental acts that are done in response to an obsession or a rigid rule with the aim of reducing anxiety. However, the extent of the compulsion

is either unrealistic or excessive. Obsessions and/or compulsions must take up at least 1 h a day, and though it may relieve their anxiety, it should not be pleasurable to the patient. In addition to the time component, the obsessions-compulsions should cause significant impairment in social or occupational functioning. The OCD symptoms should not be due to a substance or another disorder. Specifiers for OCD in the DSM 5 include the degree of insight (good, fair, poor, absent, delusional beliefs) and tic related [1].

2. Epidemiology

The 12-month prevalence of OCD in the United States is 1.2%, with similar prevalence internationally (1.1–1.8%). Females are affected at a slightly higher rate than males in adulthood; although males are more commonly affected in childhood. The mean age at onset of OCD is 19.5 years and 25% of cases start by 14 years old. Onset after 35 years is unusual but does occur. Males have an earlier age of onset than females; nearly 25% of males have onset before the age of 10. The onset of symptoms is typically gradual; however, acute onset has also been reported [1].

If OCD is untreated, the course is usually chronic, often with waxing and waning symptoms. Some have an episodic course and a minority has a deteriorating course. Without treatment, remission rates in adults are low (i.e. 20%). Onset in childhood or adolescence can lead to a lifetime of OCD. However, 40% of individuals with childhood or adolescent onset of OCD may experience remission by early adulthood. The course of OCD is often complicated by the co-occurrence of other disorders. Compulsions are more easily diagnosed in children than obsessions, because compulsions are observable. However, most children have both [1].

2.1. Prognostic factors

Greater internalizing symptoms, higher negative emotionality, and behavioral inhibition in childhood are possible temperamental risk factors. Physical and sexual abuse in childhood and other stressful or traumatic events have been associated with an increased risk for developing OCD. Some children develop the sudden onset of OCD symptoms after streptococcal infection, and subsequently it is not distinguishable from OCD for the duration of their lives. In others, it has more motor symptoms and is amenable to antibiotic treatment if it is treated immediately.

2.2. Comorbidities

Most OCD patients (76%) have a lifetime history of another anxiety disorder. Specifically, 63% have lifetime history of mood disorder, 41% have major depressive disorder, 23–32% has comorbid obsessive-compulsive personality disorder, 29% have lifetime history of tic disorder, and 12% have schizophrenia. Additional common diagnoses include bipolar, anorexia, bulimia and Tourette's [1].

2.3. Heritability

OCD may be the most heritable psychiatric condition, with a monozygotic twin concordance rate of 0.52 and a dizygotic concordance rate of 0.21, with overall heritability for OCD estimated

to be 48% [2]. The overall recurrence rate (another first degree family member getting OCD) is about 50%, which is higher with Tourette's and tics as well as childhood onset. It is lower with pure OCD of adult onset [3].

3. Current available treatment options for OCD

At the present time, exposure and response prevention should probably be the first line treatment for non-comorbid OCD. Pharmacologic interventions with significant evidence for efficacy, specifically with 8–12 weeks of medication results with greater than 30% improvement for 40–60% of OCD patients include several selective serotonin reuptake inhibitors: Fluoxetine, Paroxetine, Fluvoxamine and Sertraline in the USA; Citalopram and Escitalopram in Europe; and the tricyclic, Clomipramine.

Neurosurgery has shown promising outcomes where 58–67% of patients showed marked improvement in numerous studies even for patients who have refractory OCD (failed three medications and had 6 months of exposure and response prevention). The primary ablation anatomical targets are the fiber tracts that connect the cortex to thalamic nuclei, the anterior limb of the internal capsule and the cingulate gyrus. Nevertheless, neurosurgical procedures also yield reports of transient and persistent adverse effects [4].

Deep brain stimulation (DBS) has several advantages over ablation. Surgeons using DBS can potentially achieve a clinical effect without producing an irreversible lesion. The efficacy of ablative lesions appears to be similar to DBS.

4. Why do we need TMS for OCD?

Over 1% of the population has no improvement from current approved treatments. Even the 1% that benefits from current approved treatments is actually still quite affected by their OCD. We use improvement criteria in OCD trials rather than response and remission, similar to schizophrenia. Schizophrenia affects 1% of the population, and there are over 20 antipsychotics available in most countries. OCD affects 2.3% of the population, and there are only 5 approved medications.

5. OCD as a circuit disorder

Several inclusive models have been suggested to explain the neurobiology of OCD. One is an executive dysfunction model, where there are deficits in impulse control and inhibition of behaviors. Another is a modulatory control model, where the main dysfunction is in regulating socially appropriate behaviors. A recent model proposes OCD as an uncertainty disorder where there is an imbalance between input and input suppression [5]. Regardless of the model, there is abnormal activity in a region of the cortical-striatal-thalamic-cortical circuits. These are multiple parallel interconnected loops between cortical and subcortical areas whose role is to screen out which actions are selected and which are considered maladaptive and

ignored. These regions include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), cingulate cortex, caudate nucleus, striatum and thalamus. An abnormality in the functioning of this pathway results in impulsivity, compulsivity, obsessivity, uncertainty, deficits in attentional allocation, sensory-motor gating, modulation of motor activity and more [6, 7].

The greatest evidence for OCD as a circuit disorder comes from the success of circuit interventions at various locations along the pathway. Specifically, circuit interventions have demonstrated efficacy at the striatum, globus pallidus interna, substantia nigra, thalamus, subthalamic nucleus, anterior cingulate cortex (ACC), OFC and anterior capsulotomy [5].

6. TMS systems for OCD

6.1. Coil types

Transcranial magnetic stimulation (TMS) uses magnetic pulses to induce electrical current in the underlying neuronal tissue. There are a variety of different TMS coils on the market, and they differ primarily with the orientation and flexibility of the wire windings in the coil. Several types of coils have been used in sham-controlled OCD studies. The first is a rigid circular coil. These are typically large and very non-focal as the induced current is identical in intensity anywhere under the wire. The orientation of the current in relation to the neurons is important. The coil can be reoriented 180° to switch the direction of the current under one side of the coil, but the other side of the coil will still have an effect. The second is a figure-8 or butterfly shaped coil. This is a rigid coil, usually in a 180° plane, which induces the strongest current beneath the center of the two circular coils. However, the field decays relatively rapidly. The manufacturer for most of the research figure-8 systems is Magstim, but Magventure (formerly Medtronic) makes a double-blind figure-8 system as well. Approximately 20 companies make active figure-8 coils. An option not yet used is a bent or double cone coil, which is also a rigid coil, but it is larger and bent at a 120° fixed angle. It is capable of reaching a greater depth than a figure-8 coil. To date, it has never been used in an OCD clinical trial, but it is made by many companies similarly to the figure-8 coil. The newest coil on the market is the H7 or HAC-coil. It has flexible windings that run along the skull and sum at depth, and these windings are tightened to the head. It can reach 3 cm beneath the cortex at high frequency and high intensity; additionally, the magnetic field decays slowly. The H-coil has gaps between the central groups, which make the field different from the fixed denser distribution of the bent or double cone coil. The H7/HAC coil had the largest and only multicenter sham-controlled OCD study to date.

6.2. Cooling systems

When TMS is done repetitively (rTMS), especially at high frequencies for long periods of time, the coils will heat up. To prevent this from occurring, the coils are cooled using one of three methods; fan cooled with room temperature air (Magstim), liquid cooled (Magventure or Mag and More), or fan cooled with a forced cooled air system (Brainsway). The figure-8 coil and bent coil are available liquid cooled or fan cooled. The H-coil uses a forced air conditioning system.

6.3. Blinding system

Clinical trials with TMS ideally should include blinding for the patient, rater and operator. However, in order for the operator of the TMS device to be blinded a unique research TMS system is required. Because of this many TMS studies do not have a blinded TMS operator and the sham arm has the operator rotate the coil 90° against the scalp delivering cutaneous stimulation with the identical sound. Magventure manufactures a double-blind coil, which is in one device; then, the computer tells the operator which side of the coil to use for the patient. Magstim has separate active and sham coils. When conducting a clinical trial, one can use coil A or coil B, as well as a third coil to determine the motor threshold. Both the Magstim and Magventure, require a cutaneous nerve stimulator to induce a superficial sensation during the sham train. Some single-blind studies do not even create a cutaneous sensation at all. Brainsway has the most practical approach, since the H-coil is in a helmet both the active and sham coil is in the same helmet. The subject is assigned a card that interacts with the stimulator and coil through an interface module. The motor threshold is determined with an operator card; then the coil is advanced to the treatment position, and the subject card is inserted, which selects whether the sham or active coil is activated. The sham coil is made of conical windings that do not penetrate the cortex; so, the identical sound and a superficial sensation are felt, but no neuronal stimulation is induced.

7. Detailed review of sham-controlled trials using TMS for treatment refractory OCD

In the following paragraphs, the sham-controlled or multi-arm therapeutic studies of TMS for OCD are described in detail. For an overview, please see **Table 1**.

In 2001, Pino Alonso published a sham-controlled TMS study whereby 18 OCD patients were administered active (N = 10) or sham (N = 8) rTMS for 18 sessions (3 times a week for 6 weeks). Active and sham treatments were administered using low frequency rTMS (1 Hz, 1200 pulses) to the right prefrontal cortex (PFC) using a 70 mm circular coil. The active group was administered 110% of the left hand resting motor threshold (MT) and the sham group was administered 20%MT. Raters and patients were blinded, and operators were unaware of the expected effects of the prescribed intensity. Neither the sham nor active treatment groups had significant reduction in their OCD symptoms following 18 sessions of low frequency rTMS over the right PFC with a circular coil for 6 weeks [8].

Sachdev et al. randomly designated 12 treatment-resistant OCD subjects to right (n = 6) or left (n = 6) prefrontal rTMS treatment groups. Both groups were administered a figure-8 coil for 10 treatments over 2 weeks at 10 Hz for 1500 pulses at 110% MT. An independent rater evaluated progress once a weekly during treatment then at the 1 month follow up. In both groups, there was a significant improvement after 2 weeks and at the 1 month follow up in the obsessions, compulsions, and total scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). There was not a significant difference between left and right-sided high frequency rTMS [9].

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Alonso [8]	Magstim circular	Right PFC	1 Hz, 1200P, 110%MT Sham: 20%MT	10 8	+		+	No significant reduction in OCD
Sachdev [9]	Magstim figure 8	Right PFC Left PFC	10 Hz, 1500P, 110%MT 10 Hz, 1500P, 110%MT	6 6	- (ignorant to significance of laterality)	—	+	No significant difference between right and left high frequency. Both left and right groups had significant OCD improvement
Prasko [10]		Left DLPFC	1 Hz, 110%MT Sham	15 15				
Sachdev [11]	Magstim figure 8	Left DLPFC	10 Hz, 1500P, 110%MT Sham	10 8				
Ruffini [12]	Magstim figure 8	Left OFC	1 Hz, 600P, 80%MT Sham: (coil perpendicular to scalp)	16 7	+	—		There was a significant difference between active and sham, which lasted 10 weeks after TMS ended
Mantovani [13]	Magstim figure 8	Pre-SMA	1 Hz, 1200P, 100%MT Sham: coil with a mu shield	9 9	+	—	+	The active TMS group had 25% reduction in YBOCS compared to 12% reduction in sham
Mansur [14]	Medtronic figure 8	Right DLPFC	10 Hz, 2000P, 110%MT Sham	13 14	+	—	+	There was no difference in any of the outcome measures between active and sham
Gomes [15]	Neuro-MS figure 8	Pre-SMA	1 Hz, 1200P, 100%MT Sham	12 10	+	—	+	Significant reduction in YBOCS compared to sham
Ma [16]	α EEG guided rTMS (Cadwell 9 cm circular coil)	Midfrontal region	648–872P, 80%MT Sham	25 21	+	+	+	Significant reduction of YBOCS compared to sham

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Haghihagi [17]	Magstim figure 8	Left DLPFC	Crossover study: 20 Hz, 100%MT then sham	21	+	—	+	YBOCS improved after active rTMS
			Crossover study: sham then 20 Hz, 100%MT	21				
Elbeh [18]	Magstim figure 8	Right DLPFC	1 Hz, 2000P, 100%MT	15	+	—	+	Significant improvement compared to sham
			10 Hz, 2000P, 100%MT	15				No significant improvement compared to sham
			Sham	15				
Hawken [19]	Medtronic figure 8	SMA	1 Hz, 1200P, 110%MT	10	+	—	+	Active TMS had significant reduction in YBOCS compared to sham
			Sham: (coil rotated away from head)	12				
Seo [20]	Tamas/remed figure 8	Right DLPFC	1 Hz, 1200P, 100%MT	14	+	—	+	Significant reduction in YBOCS compared to sham
			Sham	13				
Pallanti [21]	Magstim 70-mm figure 8	SMA	1 Hz, 1200P, 100%MT	25	—	—	—	Effective in 2/3 patients.
			TAU: Antipsychotics	25				Effective in ¼ patients.
Pelissolo [22]	Magstim 70-mm figure 8	Pre-SMA	1 Hz, 1500P, 100%MT	20	+	—	+	No significant difference.
			Sham: coil with mu shield	19				
Shayganfard [23]	Magstim figure 8	Left DLPFC	Crossover study: 20 Hz, 750P, 100%MT then Sham	10	+	—	+	YBOCS improved after active rTMS
			Crossover study: sham then 20 Hz, 750P, 100%MT	10				

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Carmi [25]	Brainsway dTMS H7	dmPFC/ACC	20 Hz	16	+	+	+	Improvement compared to sham
			Sham: 20 Hz	7				
			1 Hz	8				No difference between 1 Hz & 1 Hz sham
			Sham: 1 Hz	7				
Brainsway Ltd. [26]	Brainsway dTMS H7	dmPFC/ACC	20 Hz, 2000P, 100%MT	47	+	+	+	Improvement compared to sham
			Sham	47				

Table 1. Individual characteristics of sham-controlled therapeutic TMS studies for OCD.

In 2006, Prasko conducted a sham-controlled study of 30 OCD patients, half were assigned to sham and half to active low frequency rTMS. Ten treatments over 2 weeks were administered of low frequency rTMS to the left DLPFC (1 Hz, 110% MT, total pulses not available to this author). The active group did not have any greater benefit than the sham group [10].

In 2007, Perminder Sachdev published the results of a 2-week sham-controlled study for OCD in which the patients and raters were blinded; but the operators were not. Ten subjects were randomized to active and eight to sham. High- frequency (10 Hz, 5 second train, 25 second inter-train interval, 30 trains, 1500 total pulses, at 110% of resting right hand MT) rTMS was administered to the left DLPFC in 10 sessions over 2 weeks with a figure-8 coil. Patients were offered to extend treatment up to 20 sessions. No significant difference was found between the treatment groups in YBOCS or Maudsley Obsessive-Compulsive Inventory scores after 10 sessions. There was a significant difference in YBOCS after 20 treatments; however, it was not significant after controlling for depression [11].

In 2009, Chiara Ruffini published the results of a single-blind left OFC rTMS study of 23 patients with medication resistant OCD. Using a figure-8 coil, he administered low frequency, subthreshold rTMS (1 Hz, 80% MT, 600 pulses) to the left OFC (fp1 on EEG system) with the coil parallel to the scalp for the 16 subjects randomized to active. The coil was positioned perpendicular to the scalp for the seven subjects randomized to sham. There was a significant difference between active and sham low frequency stimulation of the left OFC which lasted until 10 weeks after rTMS ended. Only one of the seven patients had a placebo response, and of the 16 active patients, four had a greater than 35% reduction in the YBOCS from baseline. It is not clear (to this writer) why no one replicated the results of this study on a larger scale, longer treatment duration in double blinded format [12].

In 2010, Antonio Mantovani published the results of a 4 week double blinded study of 1HZ rTMS to the bilateral pre supplementary motor area (SMA) at 100%MT of the thumb for 1200 pulses in 18 medication and cognitive behavioral therapy (CBT) resistant OCD patients with a figure-8 coil. The operators were not blinded, and they used a sham coil with a mu shield; but the patients and raters were blinded. On average at 4 weeks, the active TMS group had a 25% reduction in YBOCS compared to a 12% reduction in the sham group. Patients who subsequently continued an additional 4 weeks of open label treatment generally had an additional three-point decrease in their YBOCS. The results were promising but the active group only had nine completers [13].

In 2011, Carlos Gustavo Mansur published the results of a sham-controlled study of high frequency, high intensity right DLPFC rTMS for OCD using a figure-8 coil. In this study, operators were not blinded but the patients and raters were blinded. Thirteen patients received active and 14 patients received sham. rTMS was administered at 110% of resting left hand MT, 10HZ, 5 second trains, 25 second intervals, 40 trains, 2000 total pulses for 30 treatments over 6 weeks. There was no difference in any of the outcome measures between the active and sham groups [14].

In 2012, Pablo Vinicius Oliveira Gomes randomized 22 patients with moderate OCD into active (n = 12) or sham (n = 10) groups. The study was blinded to the subjects and raters; however, the TMS operators were not blinded. Patients received 10 rTMS treatment sessions

over 2 weeks utilizing a figure-8 coil with low frequency (1 Hz), 1200 pulses at 100% MT over the bilateral pre SMA. They were assessed 3 months after completing TMS. At the 2 week and 14 week assessments, the active group had a significant reduction of 35% in YBOCS scores compared to the sham group who had a 6.2% reduction [15].

In 2014, Xiaoyan Ma published a randomized single-blind sham-controlled study that enrolled 46 subjects with moderate to severe OCD. The study's goal was to determine the treatment effect of using the patient's individualized alpha electroencephalogram (α EEG)-guided rTMS (α TMS) in OCD patients. Treatment was administered with a 9 cm circular coil placed over the midfrontal region. Twenty-five OCD patients received α TMS at 80% resting MT of the hand, 4 seconds stimulation, 56 seconds interval, 20 minutes stimulation daily, total pulses varied by patient's alpha between 648 and 872 pulses per day for 10 treatment sessions over 2 weeks. Twenty-one patients received sham stimulation using an unplugged coil with acoustic effects from another coil at a distance. At the end of treatment and the 1 week follow up, the obsession component of the YBOCS was significantly reduced in the active treatment group compared to the sham group [16].

In 2015, Mohammad Haghihagi published the results of a single blinded crossover trial of 21 OCD patients. Stimulation was administered at 20 Hz, 100% resting right hand MT, 1.5 second train, 25 trains, totaling 750 pulses, 5 days a week for 2 weeks. Sham stimulation was done with the coil angled away from the skull. After 2 weeks, patients switched conditions for an additional 2 weeks. In both groups, the patient's YBOCS improved after the active rTMS condition and not during the sham condition [17].

In 2016, Khaled Elbeh randomized 45 patients into a trial to evaluate the effects of different rTMS frequencies over the right DLPFC at 100% resting left hand MT using a figure-8 coil. Fifteen patients received low frequency (1 Hz), 15 high frequency (10 Hz), and 15 received sham. The operators were not blinded. All groups were administered 10 sessions over 2 weeks of 2000 pulses each at 100% MT; then, patients were followed for 3 months post rTMS. The low frequency group but not the high frequency group's YBOCS was significantly different than sham. The effects did not last 3 months [18].

In 2016, Emily Hawken published a two-site randomized, placebo-controlled clinical trial for patients with refractory OCD using low frequency rTMS to the bilateral SMA. Ten patients received active and 12 patients were in the placebo group, where the operators rotated the coil away from the skull. rTMS was administered at 1Hz, 110% of resting hand MT, 1200 pulses for 25 sessions over 6 weeks with a figure-8 coil. Active TMS recipients obtained significant reductions in their YBOCS compared to sham. Benefits were maintained for 6 weeks after treatment [19]. This is the third small sham-controlled study showing the benefits low frequency figure-8 rTMS over the SMA.

In 2016, Ho Jun Seo published a 3-week single-blind study of low frequency rTMS to the right DLPFC with a figure-8 coil (Tamas, Remed). Fourteen patients received active and 13 patients received sham rTMS, 1 Hz, 1200 pulses, 100%MT of the left hand 5 days a week for 3 weeks. The active group had a significant YBOCS reduction compared to sham [20].

In 2016, Stefano Pallanti published the results of an open-label trial with 50 patients with SSRI refractory OCD. Patients were randomized into either the TAU (treatment as usual) ($n = 25$) or rTMS ($n = 25$) groups. The TAU group was treated with antipsychotic drugs. In the rTMS

group, patients were administered 15 sessions of rTMS over 3 weeks with a 70 mm Figure 8 coil at 1 Hz, 1200 pulses, 100%MT over the SMA. One quarter of the refractory OCD patients who were treated with antipsychotics responded compared to the subjects treated with rTMS where two thirds were responders [21].

In 2016, Antoine Pelissolo published the results of a randomized double-blind study of 40 SSRI treatment-resistant OCD patients. Subjects were randomized into active (n = 16) or sham (n = 15) groups. The patients and raters were blinded; however, the operators were not. Both groups were administered rTMS with the 70 mm figure-8 coil at 1 Hz for 1500 pulses, 100%MT to the pre-SMA for 4 weeks. The sham coil utilized a mu-metal shield over the figure-8 coil. The active group did not have a significant reduction in YBOCS compared to sham [22].

In 2017, Mehran Shayganfard published the results of a single-blind crossover study of high frequency rTMS to the left DLPFC of 10 OCD patients using a figure-8 coil. Stimulation was administered at 20 Hz, 100% resting right hand MT, 1.5 second train, 25 trains, totaling 750 pulses, 5 days a week for 2 weeks. Sham stimulation was done with the coil angled away from the skull. After 2 weeks, patients switched conditions for an additional 2 weeks. In both groups, the patient's YBOCS improved after the active rTMS condition and not after the sham condition [23, 24]. This was the second single blinded study this group did with the same crossover after 2 weeks [17, 23]. Methodologically, they should do a double-blind non-crossover study, and at a significantly later date offer the sham patients active treatment.

Between 2012 and 2014, a feasibility study used an H-coil designed to target the medial prefrontal cortices and anterior cingulate cortices (ACC) bilaterally (HAC or H7 coil) in 41 treatment-resistant obsessive-compulsive-disorder (OCD) patients with moderate to severe symptoms. Treatments were administered after the patient's individual symptoms were provoked, and improvements were measured using the YBOCS. Initially the study had four arms, a high frequency arm of 20 Hz, a sham 20 Hz arm, a low frequency arm of 1 Hz and a sham 1 Hz arm. Because the interim analysis showed no difference between the sham and 1 Hz arms, the study was continued with just high frequency and sham. At the end of the study, the response rate in the 20 Hz arm was much greater than in the sham group and the improvements were still present a month after treatments ended [25, 26].

Subsequently, from 2014 to 2017 94 patients with moderate to severe treatment-resistant OCD were randomized in a multicenter double-blind study to either 20 Hz active or sham dTMS, at 100% resting MT of the foot, 2 second trains, 20 second inter train intervals, 2000 total pulses per day. Treatments were administered daily for 29 days over 6 weeks after the patient's individual symptoms were provoked, with a follow up at week 10. Although the study has been completed with a public announcement of positive results, the details have not been published yet.

8. Conclusion-key results

OCD is uniquely suited for intervention with TMS. However, rTMS interventions in OCD that focus on the lateral prefrontal cortices in both high and low frequency are not consistently efficacious. Most of the small sham-controlled studies treating the SMA, left DLPFC, and right DLPFC with low frequency as well as high frequency showed benefit. This is consistent with

the results of a recently published meta-analysis. The meta-analysis noted the right DLPFC had a greater therapeutic effect than other treatment locations [27]. The next step should be a fully blinded (including the operators) sham-controlled multicenter study of low frequency rTMS to the SMA (the pre-SMA is the anterior portion of the SMA, and it is a midline region so it is always treated bilaterally even with a figure-8 coil). Two high frequency, high intensity studies using the HAC/H7 deep rTMS coil showed efficacy for OCD including a multisite study for FDA clearance. We await the detailed presentation of those results.

Further directions for the field include optimizing stimulation parameters for greater efficacy. What state should the circuitry be in during the stimulation? Does the treatment have durability or is maintenance necessary? If children and adolescents are treated early will it change the trajectory of their illness? Does the same protocol work for OCD related disorders such as hoarding, trichotillomania and body dysmorphic disorder? Does this work for OCD without insight or with delusions? Does it help with tics? What happens to the neural circuitry of the OCD patients responding to TMS? Can non-responders benefit from an individualized protocol? Can we predict responders from non-responders before we go through an entire treatment course?

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