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RESEARCH ARTICLE

TREATMENT-RESISTANT OBSESSIVE COMPULSIVE DISORDER: AN EVALUATION STUDY OF THE AUGMENTATION EFFECT OF LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

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Abstract

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Background: Thelifetime prevalence of obsessive-compulsive disorders (OCD) is estimated to be around 3% in the general population. Selective serotonin reuptake inhibitors (SSRIs) are considered to be the primary treatment strategy of OCD in addition to psychotherapy. Unfortunately, current medications, augmentation strategies, and behavioral therapies fail to provide adequate benefits in many cases. A large percentage of patients (40-60%) do not show satisfactory response to the standard treatments, some of them experiencing a chronically deteriorating course, leading to marked interpersonal and occupational impairments. In recent years, non-invasive neuromodulatory techniques such as repetitive transcranial magnetic stimulation have been increasingly studied as potential adjunct or alternative therapies for a wide range of neurological and psychiatric conditions including pain disorder, depression, and stroke rehabilitation and OCD.

Aims: the aim of this work to evaluate rTMS as an augmentation strategy in treatment-resistant OCD, to test the potential value oflow frequency rTMS to SMA,orbitofrontal cortex and right DLPFC in the treatment of resistant OCD and to compare between the therapeutic values of applying the TMS coil to those different areas of the cortex.

Patients and Methods: This study was carried out in Psychiatry, Neurology and Neurosurgery Center, Tanta University from September 2017 to November 2019. Eighty patients (52 females and 28 males) aging between 18 and 65 years underwent complete psychiatric evaluation, including full medical history, psychiatric and physical examination and diagnosed as having OCD accordingto DSM-5 with failure of at least two adequate therapeutic trials of SRIs.

Results: Before rTMS sessions there was no statistical significant difference between the three active groups and the sham group regarding the scores onYale-Brown obsessive compulsive scale,Hamilton anxiety rating scale, Hamilton depression rating scale and Clinical global impression scale. Results after rTMS sessions

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revealed the following: Active rTMS on the SMA, the left OFC and right DLPFC was associated with marked improvement in YBOCS, Hamilton anxiety rating scale, Hamilton Depression rating scale and clinical global impression scale. The most significant improvement in Yale Brown Obsessive Compulsive scale was obtained when the brain target was the SMA. The most significant improvement in anxiety rating scale and depression ratingscale was obtained when the brain target was the left OFC. Sham group didn't have significant improvement through the study.

Conclusions: We can thus conclude that low frequency rTMS is significantly effective as an adjunctive treatment for resistant OCD and that the SMA is the most effective brain target.

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Introduction:-

Obsessive compulsive disorder (OCD) is a disabling psychiatric disorder characterized by obsessions and compulsions. Obsessions are ego-dystonic, unwanted thoughts,images or impulses that repeatedly enter one's mind. Compulsions are repetitive, time-consuming behaviors or mental acts performed to neutralize the anxiety provoked by obsessions **(Heyman et al., 2006)**.

Obsessive-compulsive disorder (OCD) is a highly debilitating condition with a lifetime prevalence of 2%-3% **(Ruffini et al., 2009)**.Up to 40-60% of obsessive-compulsive disorder (OCD) patients do not have a satisfactory outcome with currently available treatments **(Pallanti et al., 2002, Simpson et al., 2006).**

Treatment-resistant OCD has been described as the failure of at least two adequate therapeutic trials of SRIs **(Goodman et al., 2000)**. Drug-resistant OCD literature indicates an absence of a reduction in YBOCS scores (more than 35%) after at least 2 trials with SSRIs and 1 trial with clomipramine **(Ruffini et al., 2009).** The term treatment refractory implicates a greater degree of resistance **(Husted and Shapira 2004).**

Repetitive TMS is a noninvasive technique that generates repetitive, brief and powerful magnetic pulses by stimulating coil applied over the scalp that induces an electric current in the brain.rTMS is affected by parameters such as intensity, frequency, pulse number and duration. High frequency (more than 5 Hz) rTMS promotes cortical excitability, while low frequency (less than 1 Hz) rTMS inhibits cortical excitability **(Lee et al., 2017)**

Two studies have been previously conducted in the center of psychiatry, neurology and neurosurgery to evaluate rTMS use in the treatment of OCD; in one of them rTMS was addressed to the right DLPFC **(Abohamar et al., 2008),** while in the other, the left DLPFC was the stimulation site **(Badawy et al., 2010).** In both of them high frequency rTMS (20 Hz) was used.A study by**Haghighi et al., (2015)** targeted bilateral DLPFC with high frequency stimulation.

Elbeh and his colleagues (2016)used low frequency stimulation on the right dorsolateral prefrontal cortex. They compared the effect of low (1 Hz) and high (10 Hz) rTMS in matched groups of patients. They found that the effect of 10 Hz did not differ from sham while 1 Hz rTMS over right DLPFC improved OCD symptoms more than sham.These results are in line with several studies demonstrating no significant long lasting change in OCD symptoms after application of high frequency rTMS**(Greenberg et al., 1997, Sachdev et al., 2001, Sarkhel et al., 2010).**

There have been several studies using rTMS in treatment-resistant OCD. Those studies used low frequency stimulation. Among them, there were:

(1)Studies targeting the left orbitofrontal cortex which corresponds to Fp1 (International 10-20 EEG system) **(Ruffini et al., 2008)** and (2) Studies targeting the supplementary motor area (SMA) bilaterally. Pre-SMA was defined at 15% of the distance between inion and nasion anterior to Cz (vertex) on the saggital midline. The coil was placed with the handle along the saggital midline, pointing towards theocciput to stimulate bilaterally and simultaneously the pre-SMA**(Mantovani et al., 2010, Lee et al., 2017).**

Clinically significant improvement in OCD symptoms was found in drug-resistant OCD patients with benefits lasting up to 10 weeks after the end of rTMS treatment **(Ruffini et al., 2009)**.

Treatment-resistant OCD has a devastating effect on the patient's life, and its treatment is an obvious challenge to psychiatrists. Repetitive transcranial magnetic stimulation is a promising tool in the diagnosis and management ofneuropsychiatric disorders and many studies recommend further investigations of its optimal use.

Patients and Methods:-

This study was carried out in Psychiatry, Neurology and Neurosurgery Center, Tanta University from September 2017 to November 2019.

80 patients (52 females and 28 males) aging between 18 and 65 years underwent complete psychiatric evaluation, including full medical history, psychiatric and physical examination and diagnosed as having OCD accordingto DSM-5 with failure of at least two adequate therapeutic trials of SRIs.

Inclusion criteria:

1. All patients meet the DSM-5 criteria for OCD with failure of at least two adequate therapeutic trials of SRIs. An adequate therapeutic trial is defined as treatment for at least 12 weeks on the SRI, that meets or exceeds recommended dosage level for OCD.
2. The age of the patients is between 18-65 years.
3. Both males and females are included

Exclusion criteria:

1. Major medical or neurologic conditions.
2. A history of seizure or bearing pacemakers.
3. Intellectual disability (IQ less than 85)
4. Patients with psychosis, bipolar disorder, brain injury.
5. Patients with pregnancy or breast feeding.

Methods:-

The 80 patients included in the study have been randomly divided into two groups:
The first group of patients consisting of 60 patients have been treated using augmentation by 1 Hz rTMS.

This group has been furtherly randomly classified into three subgroups 20 patients each:
The first subgroup received 20 sessions of 1Hz rTMS. Each session consisted of a 20-minute train (1200 pulses/ day) at 100% of resting MT.

The coil was positioned over pre-SMA.
Pre-SMA was defined at 15% of the distance between inion and nasion anterior to Cz (vertex) on the saggital midline.

The coil was placed with the handle along the saggital midline, pointing towards the occiput.

The patients received the sessions once a day, 5 days a week, for 4 weeks, resulting in 20 sessions **(Mantovani et al., 2010; Lee et al., 2017).**

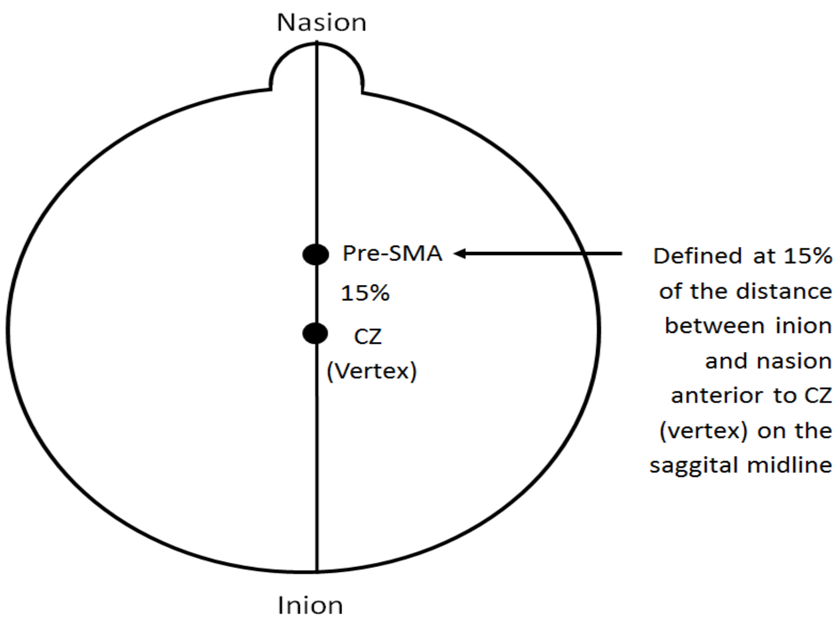

Figure (1):- To illustrate how the pre-SMA area is defined.

Thesecondsubgroup received 15 sessions of 1Hz rTMS.

The brain target was the left OFC, which corresponds to Fp1 (International 10-20 EEG system)
The patients received 10-minutes of 1Hz left-sided subthresholdrTMS (intensity 80% of the resting motor threshold) over the left frontopolar cortex targeting the OFC for 15 sessions(1 session per day, 5 sessions per week, for 3 weeks) (**Ruffinietal**., **2009**).

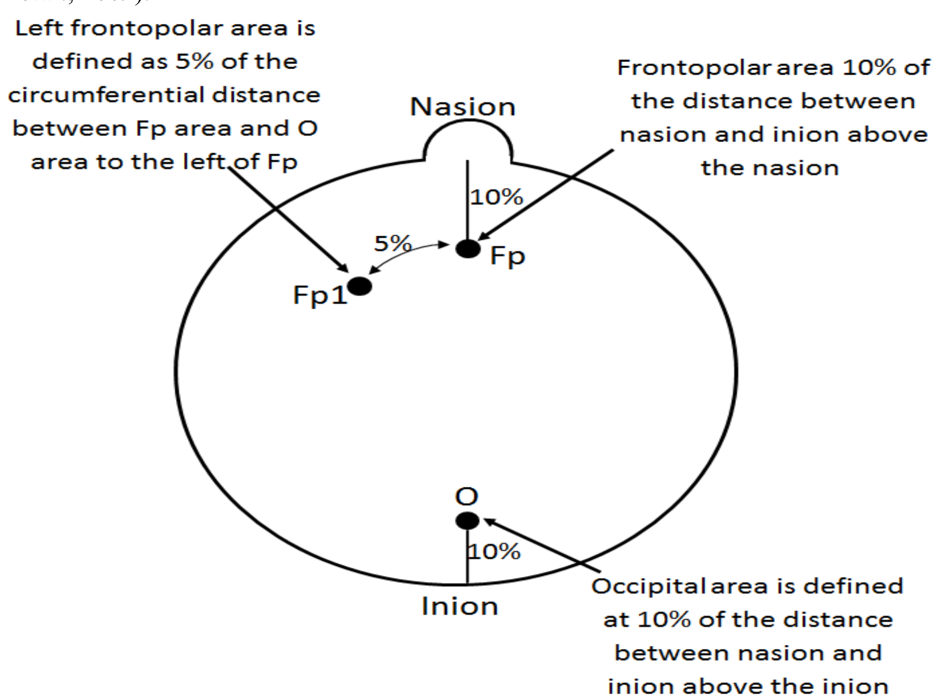

Figure (2):- To illustrate how the left OFC area is defined.

The third subgroup of patients received 10 sessions of 1 Hz rTMS. The brain target was the Right DLPFC. The DLPFC stimulation site was defined as the region 5 cm rostral in the same saggital plane as the optimal site for MT production in the first dorsal interosseous. For each patient 10 sessions were administered once a day for 5 consecutive days each week for two weeks **(Elbeh et al., 2016).**

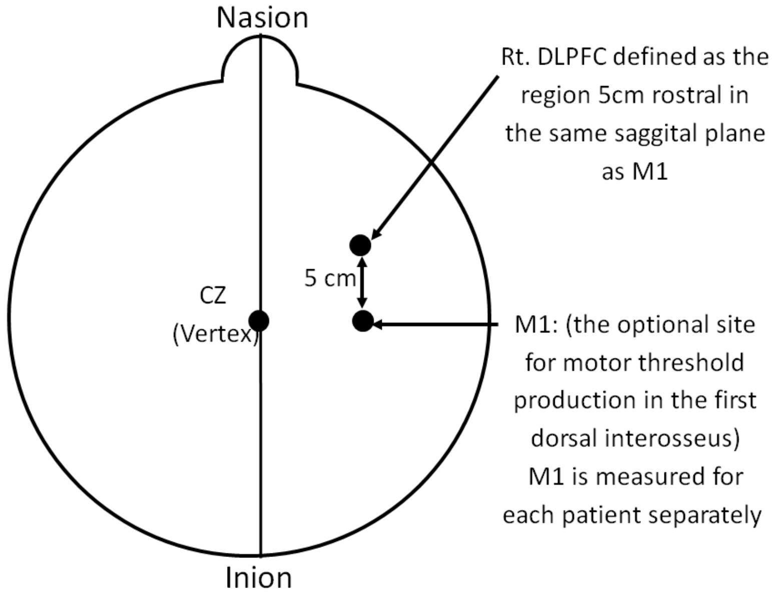

Figure (3):- To illustrate how the Rt. DLPFCarea is defined.

Statistical analysis:
The collected data were organized, tabulated and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. The level of significant was adopted at p<0.05.

Results:-

Table (1):- Comparison of Yale-Brown obsessive compulsive scale (Y-BOCS) among participants before and after treatment .

Type of treatment	Y-BOCS (Mean+SD)			t	p
	Before	After	Difference		
DLPFC	33.90+8.14 20-40	25.50+13.65 2-40	-8.40+8.20 -20-0.0	4.583	0.001*
Left OFC	34.40+7.50 22-40	24.00+13.92 10-40	-10.40+9.2 -20-0.0	5.048	0.001*
SMA	35.40+6.24 15-40	21.70+14.09 0-40	-13.70+13.14 -31-0.0	4.662	0.001*
Sham	34.80+6.34 25-40	34.80+6.34 25-40	0.0 0.0	-------	-------
F	0.160	4.281			
p	0.923	0.008*			

*Significant

Table (1) shows the mean score of Yale Brown obsessive compulsive scale before and after different interventions. All treatment regimen, except sham group, showed improvement in total score of Yale Brown obsessive compulsive scale. This improvement is evident by the decreased total score after intervention. The maximum improvement was recorded for the SMA group with a decrease of 13.7+13.14 followed by left OFC showing a decrease of 10.40+9.2. Lastly DLPFC showed the lowest difference of the scale before and after intervention (8.40+8.20). All these differences were found statistically significant at p=0.001. Difference of the mean value of the Yale Brown scale before intervention between the different treatments regimens were not found statistically significant. Meanwhile,

difference of the Yale brown scale after intervention were statistically significant between different treatment groups p=0.008

Table (2):- Comparison of Hamilton anxiety rating scale among participants before and after treatment .

Type of treatment	Hamilton anxiety rating scale			t	p
	Before	After	Difference		
DLPFC	22.00+8.66 8-41	15.10+11.71 2-41	-6.90+4.36 -13-0.0	7.071	0.001*
Left OFC	20.40+11.47 3-36	8.80+6.17 0-16	-11.60+11.58 -32-0.0	4.479	0.001*
SMA	22.95+7.05 9-33	14.35+11.67 0-33	-8.60+7.96 -20-0.0	4.834	0.001*
Sham	24.40+4.18 20-30	24.40+4.18 20-30	0.0 0.0	-------	-------
F	0.824	10.175			
p	0.485	0.001*			

*Significant

Table (2) shows results of intervention on Hamilton anxiety rating scale. Before intervention the difference between patients in different treatment groups were not statistically significant. However, after intervention results were statistically significant between different treatment groups (p=0.001). Within each group, difference of the Hamilton scale was significantly decreased as compared to before intervention. The largest decrease of the scale was reported for left OFC with a mean of 11.60+11.58. This followed by SMA (8.60+7.96) and DLPFC (6.90+4.36). All these differences in treatment groups were statistically significant. Within the sham group, no statistically significant difference was recorded after intervention as compared to before intervention.

Table (3):- Comparison of Hamilton depression rating scale among participants before and after treatment.

Type of treatment	Hamilton depression rating			t	p
	Before	After	Difference		
DLPFC	22.60+10.06 2-38	15.40+11.02 0-38	-7.20+5.98 -16-0.0	5.385	0.001*
Left OFC	22.40+8.84 10-36	10.60+6.73 2-18	-11.80+8.86 -24-0.0	5.957	0.001*
SMA	22.65+9.58 10-38	14.25+12.44 0-38	-8.40+7.80 -21-0.0	4.814	0.001*
Sham	24.00+10.52 11-39	24.00+10.52 11-39	0.0 0.0	-------	-------
F	0.113	5.956			
p	0.953	0.001*			

*Significant

Table (3) shows results of Hamilton depression rating scale before and after intervention in relation to different treatment groups. Within each group, difference were found statistically significant. The left OFC group showed the largest difference of Hamilton depression scale where it decreased by 11.80+8.86 after intervention as compared to pre-intervention (p=0.001). The differences between the observation before intervention and after intervention were 8.40+7.80 for SMA and 7.20+5.98 for DLPFC where both differences were statistically significant at p=0.001. Differences before intervention between treatment groups were not significant while they were significantly different after intervention (p=0.001)

Table (4):- Comparison of clinical global impression-severity scale among participants before and after treatment.

Type of treatment	Clinical global impression-severity scale			t	p
	Before	After	Difference		
DLPFC	5.50+0.69 4-6	4.60+1.46 2-6	-0.90+0.97 -3-0.0	4.158	0.001*
Left OFC	5.80+0.77 5-7	4.40+1.54 3-7	-1.40+0.82 -2-0.0	7.628	0.001*
SMA	5.95+0.51 5-7	4.25+1.83 0-7	-1.70+1.75 -6-0.0	4.344	0.001*

Sham	5.40+0.82 4-6	5.40+0.82 4-6	0.0 0.0	-------	-------
F	2.628	2.459			
p	0.056	0.069			

*Significant

Results of clinical global impression scale are shown in table (4). Within each treatment group a significant improvement was recorded as shown by decrease in the scale score after intervention compared to before intervention. The best improvement was seen in SMA groupshow in a mean decrease of 1.70+1.75 then left OFC (1.40+0.82) and DLPFC (-0.90+0.97). All these differences were found statistically significant (p=0.001). On the other hand both results before intervention and after intervention were not different in relation to different treatment groups.

Discussion:-

The present study was conducted at Psychiatry, Neurology and Neurosurgery Center, Tanta University.It was conducted with the aim of evaluating the effect of low frequency rTMS on the treatment of resistant OCD and comparing the efficacy of stimulating different cortical targets.

This study is a randomized controlled study in which 80 patients with treatment resistant OCD fulfilling the inclusion and exclusion criteria were selected. The 80 patients were randomly assigned to 60 patients who received real TMS and 20 patients who received sham stimulation. The active group was furtherly randomly assigned to three groups: the first group received rTMS on the SMA, the second group on the OFC and the third group on the right dorsolateral prefrontal cortex.

Inthe present study we postulated that because OCD may be related to increased neural activity in prefrontal subcortical circuits, then it might be susceptible to treatment using an inhibitory rTMS protocol (Whiteside et al., 2004). The three targeted areas have been mentioned as promising in multiple recent papers and reviews. (**Saba et al., 2015, Elbeh et al., 2016, Lee et al., 2017)** We compared active rTMS on the three cortical targets with sham and we compared between the efficacy of applying rTMS coil on each of the three targets.

Before rTMS sessions the 4 groups were matched in terms of Yale-Brown obsessive compulsive scale, Hamilton anxiety rating scale, Hamilton depression rating scale and Clinical global impression scale. There was no significant difference between the 4 groups.

Our study shows that active rTMS on the SMA, the left OFC and right DLPFC was associated with markedimprovement in YBOCS, Hamilton anxiety rating scale, Hamilton Depression rating scale and clinical global impression scale.The Yale-Brown obsessive compulsive scale improved in all its 10 items (Time spent on obsessions, interference from obsessions, distress of obsessions, resistance to obsessions, control over obsessions, time spent on compulsions, interference from compulsions, distress from compulsions, resistance to compulsions, control over compulsions).

Saba and his colleagues (2015)investigated the efficacy of transcranial cortical stimulation in the treatment of obsessive-compulsive disorders. The results show that high frequency r-TMS over the DLPFC does not seem to be an effective option for the treatment of OCD. Even if the reductions of Y-BOCS scores are significant, there were no differences with sham stimulation**.**

Conversely, stimulation of SMA and OFC using low frequency rTMS provides statistically significant superiority of active compared to sham stimulation in several studies **(Mantovani et al.,2013).**

The efficacy of low frequency rTMS on OC symptoms might be explainedby the inhibitory effect of low frequencies on hyperactive orbitofronto-striatal circuits that seem to underlie deficient inhibition of irrelevant information and response control in OCD **(Berlim et al., 2013).**

Our study shows that active rTMS improved the scores on YBOCS. All treatment regimen, except sham group, showed improvement in total score of Yale Brown obsessive compulsive scale. This improvement is evident by the decreased total score after intervention. The maximum improvement was recorded for the SMA group with a decrease of 13.7+13.14 followed by left OFC showing a decrease of 10.40+9.2. Lastly DLPFC showed the lowest difference of the scale before and after intervention (8.40+8.20). All these difference were found statistically significant at p=0.001.

The SMA is related to motor planning and response-inhibition **(Mostofskyand Simmonds, 2008)** and is also connected with several regions widely implicated in cognitive and emotional processes **(Oliveri et al., 2003).** The hypothesis is that inhibiting areas such as pre-SMA or OFC may alleviate OCD related-symptoms by modulating hyperactivity of cortico-striato-thalamo-cortical circuitry**.**In other words, low frequency rTMS induced normalization of SMA/OFC activity could have enhanced the ability of patients with OCD to inhibit intrusive thoughts, impulses and repetitive motor responses **(Montovani et al., 2013).**

Our study shows that active rTMS improved the scores on Hamilton anxiety rating scale. After intervention results were statistically significant between different treatment groups (p=0.001). Within each group, difference of the Hamilton scale were significantly decreased as compared to before intervention. The largest decrease of the scale was reported for left OFC with a mean of 11.60+11.58. This followed by SMA (8.60+7.96) and DLPFC (6.90+4.36).

Our study also shows that active rTMS improved the scores on Hamilton depression rating scale. The comparison of the 4 groups after TMS revealed significant difference between the 3 active groups and the sham group (p=0.001). Within each group, difference were found statistically significant. The left OFC group showed the largest difference of Hamilton depression scale between before and after intervention where it decreased by 11.80+8.86 after intervention as compared to pre-intervention (p=0.001). The differences between the observation before intervention and after intervention were 8.40+7.80 for SMA and 7.20+5.98 for DLPFC where both differences were statistically significant at p=0.001.

Our findings differ from the results of multiple previous studies which investigated the efficacy of DLPFC in the treatment of depression and reported greatest improvements in depressive symptoms when high frequency rTMS was applied over the DLPFC **(Kedzior et al., 2014),** whereas our study found the greatest improvement in depressive symptoms following low frequency rTMS applied over the left OFC.

Our findings differ from the findings of **Lee et al., (2017)** who stated that except for OCD symptoms decrease, rTMS on the SMA showed no significant anti-depressant and/or anxiolytic effects. Our study showed that low-frequency rTMS had an antidepressant and anxiolytic effects: specifically the OFC had the most effective anxiolytic effect and antidepressant effect.

Our results are in concordance with the study of **Pallanti et al., (2016)**who administered low-frequency rTMS on the SMA and found that along with the decrease of Y-BOCS total score during rTMS treatment, a similar trend was also seen for the HAM-D total score. This seems to confirm the strong link between OCD and depressive symptomatology. A type of hierarchic relationship between the two disorders has been recently proposed **(Marazziti et al., 2008)**. The rationale of this hypothesis is constituted by the consideration that the remission of depressive symptoms is generally not followed by an amelioration in OCD symptoms, whereas the stabilization in OCD seems to have a beneficial effect on depression**(Pallanti et al.,2016).**

Our study shows that active rTMS on the SMA and the DLPFC and left OFCimproved the scores on Clinical global impression scale. The best improvement was seen in SMA groupshowinga mean decrease of 1.70+1.75 then left OFC (1.40+0.82) and DLPFC (-0.90+0.97). All these differences were found statistically significant (p=0.001).

Recent neurophysiological andneuroimaging studies suggest that premotor and motor areas are hyperactive in OCD **(Yücel et al., 2007)**. However it is not known whether this hyperactivity represents part of OCD pathophysiology, or whether it may represent a compensatory mechanism. **(Mantovani et al., 2010)**

Our findings are in accordance with the findings of Simone **Rehn et al (2018)**who found in a meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder, they found that rTMS applied over the SMA yields greater improvements in OCD severity than rTMS applied over the DLPFC or OFC, which has not been found in previous meta-analyses. This may be attributed to the inclusion of two recent studies targeting the SMA with rTMS. Given that a large reduction in OCD severity following rTMS treatment was found in **Hawkin et al (2016)**, the inclusion of this study may have contributed to the significant advantage of SMA target over other cortical targets, found in the meta-analysis by **Rehn et al., (2018)**. While **Berlim et al., (2013)**identified the SMA and OFC as more promising rTMS targets for treating OCD than the DLPFC, the meta-analysis by **Rehn et al., (2018)**revealed that targeting the SMA yielded significant improvements in OCD symptoms, whereas active rTMS targeting the OFC was not more effective thanshamrTMS. Although studies targeting the OFC and SMA remain scarce, which limits our ability to draw conclusions, the meta-analysis by Rehn et al (2018) and our study extend existing research by clarifying the differing effectiveness of rTMS in OCD when applied over different cortical regions **(Rehn et al., 2018).**

The SMA appears to be the most effective cortical target in the treatment of OCD using rTMS, and this is attributed to the normalization of hyperactive orbitofronto-striatal circuits induced by low frequency rTMS**(Mantovani et al., 2010).** The SMA plays a central role in motor planning and response-inhibition **(de Wit et al., 2012)**, and has extensive connections to regions involved in cognitive and emotional processes **(Oliveri et al., 2003).** Studies suggest that hyperactivity in this area may be associated with deficient inhibitory control over repetitive behaviors that patients with OCD display **(Yücel et al., 2007)**, thus making it an attractive target for the inhibitory effects of low frequency rTMS. In support of this, motor-pathway excitability increases from baseline after low frequency rTMS, demonstrating increased cortico-subcortical inhibition, and is associated with beneficial responses in patients with OCD **(Mantovani et al., 2010).** Furtherrmore, cortical excitability studies have found that low frequency rTMS applied over the pre-SMA increased inhibition in the primary motor cortex, which was correlated with effective clinical response in OCD symptoms **(Mantovani et al., 2013)**.Therefore, it appears that low frequency rTMS targeted at the SMA may have assisted patients with OCD to inhibit repetitive motor responses and improve OCD symptoms by restoring cortical inhibition. **van den Heuvel et al., (2009)** has also reported that different brain areas may be involved in OCD depending on the specific OCD symptom, e.g. harm/ checking symptoms versus contamination/cleaning symptoms. Thus, future studies should attempt to examine the relationship between treatment response after stimulation of different anatomical areas and specific OCD symptoms**(Rehn et al., 2018).**

Low frequency rTMS has also been used to normalize hyperactivity in the OFC as it is associated with deficient control over intrusive thoughts, impulses, or urges present in OCD **(Saba et al., 2015)**. However, the OFC is located deep beneath the scalp and is difficult to stimulate with conventional rTMS devices **(Nauczycielet al., 2014).** Our findings show that rTMS applied over the OFC was the second most effective cortical target reguarding improvement in the Yale-Brown obsessive-compulsive scale. These findings differ from the results of the meta-analysis by **Rehn et al., (2018)**who found that rTMS applied over the OFC was not significantly more effective than sham rTMS, however it is to be noted that the subgroup reguarding OFC only consisted of two RCTs in the meta-analysis by **Rehn et al., (2018)**, thus they stated that the effectiveness of the OFC as a cortical target for rTMS cannot be concluded**(Rehn et al., 2018).**

Our findings differ from the results of **Pelissolo et al., (2016)** who found in a sham-controlled study that low-frequency rTMS delivered to pre-SMA during 4 weeks had no better effects on drug-refractory OCD patients than sham stimulation.

Recommendations:-

1. We recommend the use of low-frequency repetitive transcranial magnetic stimulation as an adjunctive treatment for resistant OCD.
2. We recommend the Supplementary motor area as a brain target for stimulation.
3. We recommend the left orbitofrontal cortex as a brain target for treatment of anxiety and/or depression.
4. Future studies should investigate larger sample size and longer follow up periods.

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