Journal of Psychiatric Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Functional connectivity changes and symptoms improvement after personalized, double-daily dosing, repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A pilot study

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ARTICLE INFO

Keywords:
Obsessive compulsive disorder
Neuromodulation
rTMS
Supplementary motor area

ABSTRACT

Background: intrusive thoughts and compulsive behaviors that characterize obsessive compulsive disorder (OCD) are associated to aberrant resting state functional connectivity (rsFC) patterns within the cortico-striatal-thalamo-cortical (CSTC) circuits. A high percentage of OCD patients do not respond to conventional pharmacological treatments or psychotherapy. In these patients, inhibitory repetitive transcranial magnetic stimulation (rTMS) of the Supplementary Motor Area (SMA) resulted in a significant clinical benefit.

Methods: In the current study, we applied a novel protocol of 1-week MRI-guided individualized double-daily sessions of rTMS treatment (1-Hz; 110% of resting Motor Threshold/7200 pulses/day), to bilateral SMA in 9 OCD patients. We tested its (i) feasibility-safety, (ii) clinical efficacy and (iii) rsFC related changes.

Results: Patients reported no side effects during and after rTMS. Personalized rTMS treatment led to a significant improvement of OCD symptoms (average 25%; $p = .005$) and persistence of benefit up to 3-month follow-up. rsFC analysis revealed a significant reduction of connectivity patterns between bilateral SMA and subcortical regions, specifically in the basal ganglia and thalamus. Additional analysis showed that OCD symptoms severity correlates with a higher connectivity pattern between bilateral SMA and subcortical regions.

Conclusions: rTMS double-daily sessions are safe, feasible and effective in OCD. The clinical outcomes, that are consistent with those found in our previous RCT, are linked to a decreased connectivity between SMA and subcortical brain areas implicated in control over obsessions and maladaptive compulsive behavior.

1. Introduction

Obsessive compulsive disorder (OCD) is a disabling psychiatric condition consisting of a heterogeneous combination of intrusive thoughts, repetitive behaviors or mental acts (5th ed.; DSM –5; American Psychiatric Association, 2013). The disease has a life-time prevalence of 2% (Ruscio et al., 2010) with a late childhood or early adulthood onset (Lijster et al., 2017) and the symptomatology frequently affects socialization and working functionality (Subramaniam et al., 2013).

Specific dysfunctions of the cortico-striatal-thalamo-cortical (CSTC) brain circuits are involved in the disorder (Rădulescu et al., 2017; Rapinesi et al., 2019). The CSTC pathways include both dorsal and medial areas of the prefrontal cortex such as the dorsolateral prefrontal cortex (DLPFC) the orbitofrontal cortex (OFC), the supplementary motor area (SMA) and subcortical structures such as the thalamus and the basal ganglia (Lusicic et al., 2018; Milad and Rauch, 2012). Two main pathways of communication have been identified (Alexander et al., 1986); (i)

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https://doi.org/10.1016/j.jpsychires.2020.10.030
Received 15 July 2020; Received in revised form 19 October 2020; Accepted 23 October 2020
Available online 29 October 2020

a direct or positive feedback pathway, emerging from the cortex with glutamatergic projections directed to the basal ganglia, decreasing the inhibitory action of the pars interna of the globus pallidus and consequently increasing the thalamo-cortical drive; (ii) an indirect or negative feedback pathway, projecting from the globus pallidus to the thalamus through three inhibitory and one excitatory synapse, so resulting in a reduced thalamo-cortical output (Saxena and Rauch, 2000; Maia et al., 2008). One section of the CSTC circuit has been implicated in OCD pathophysiology and it includes the projections from premotor and sensorimotor cortical areas to the striatum (Krack et al., 2010).

The abnormal presence of ruminative thoughts and repetitive behaviors might be associated to the malfunctioning of the direct sensory-motor CSTC loop or to an imbalance between the direct and the indirect pathways (Baxter et al., 2001; Maia et al., 2008; Russo et al., 2014): in OCD patients, this is reflected by a hyperexcitability of the motor circuit, particularly of the SMA (Yücel et al., 2007). According to a paired-pulse TMS protocol, a decreased inhibitory intracortical activity could represent a possible consequence of hyperexcitable cortical and subcortical structures in these patients (Greenberg et al., 1998). Moreover, somatosensory gating during voluntary movements is reduced in OCD, together with increased amplitude of sensory evoked potentials (SEP) in precentral areas (Rossi et al., 2005), suggesting a deficit to integrate sensory-motor information due to a tonic hyperactivity of brain premotor areas.

Neuroimaging findings confirm the role of CSCT circuit dysfunction in the pathogenesis of OCD (Whiteside et al., 2004). A greater SMA activity is detectable during the execution of the Multi-Source Interference Task (Yücel et al., 2007) and the higher BOLD signal pattern within the CSTC circuit is linked to the failure of achieving a goal and to perseverative/maladaptive action repetition in OCD patients (Apergis--Schoute et al., 2017). Moreover, the SMA hyperactivation has been associated with inhibitory response process in OCD (de Wit et al., 2012) and the higher amplitude of the Error Related Negativity, detected with the EEG after an error execution, positively correlates with the SMA activation (Grützmann et al., 2016), confirming the role of a dysfunctional conflict monitoring and an excessive attention to the response, representing a compensatory mechanism for dysfunctional prefrontal activations or primarily characterizing OCD pathology (Corbit et al., 2019).

In addition, altered patterns of resting-state functional connectivity (rsFC)have been highlighted in OCD patients. This aberrant communication involves premotor and motor cortex, subcortical regions, and cerebellum (Apergis-Schoute et al., 2018; Sha et al., 2020), thus encompassing wide rsFC dynamics of the whole motor network. In drug-naïve OCD patients, an increased rsFC between the SMA and putamen is observed (Zhao et al., 2017), explaining the presence of hyperexcitability of CSTC circuit. Successful OCD treatments, often consisting of a combination of serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) (Abramowitz et al., 2006;Koran et al., 2007; Hirschtritt et al., 2017) are linked to the normalization of the BOLD signal in brain areas within the CSCT circuit (Lázaro et al., 2008; Atmaca, 2013). Unfortunately, approximately 40% of patients remain significantly symptomatic despite appropriate treatments (Pallanti et al., 2002; Pallanti and Quercioli, 2006).

In recent years, non-invasive-brain-stimulation (NIBS) techniques have been increasingly used, in psychiatric patients (Sauvaget et al., 2018); in this context, several NIBS protocols for the treatment of OCD patients have been developed, either using transcranial direct current stimulation (tDCS) (D'Urso et al., 2018 () or rTMS (Trevizol et al., 2016) and a deep variant of rTMS has also been FDA-approved for OCD treatment (Carmi et al., 2019).

Concerning the traditional rTMS protocols, the bilateral DLPFC (Greenberg et al., 1997), the right OFC (Ruffini et al., 2009) and the pre-SMA/SMA (Mantovani et al., 2010a) have been targeted in OCD patients, based on the dysfunctional cognitive/sensorimotor CSTC (Lusicic et al., 2018). Despite some encouraging results (Jahangard et al., 2016; Nauczyciel et al., 2014; Ruffini et al., 2009; Seo et al., 2016), the clinical efficacy of rTMS on DLPFC and OFC is lower (Alonso et al., 2001; Mansur et al., 2011; Sachdev et al., 2007; Sarkhel et al., 2010; Ma et al., 2014; Saba et al., 2015; Rapinesi et al., 2019; Lefaucheur et al., 2020) than that of rTMS on SMA (Cocchi et al., 2018; Rehn et al., 2018), though discordant outcomes have been reported (Kang et al., 2009; Pelissolo et al., 2016).

Inhibitory rTMS on SMA (at the pre-SMA/SMA junction) reduces OCD symptoms (Mantovani et al., 2006, 2010a, 2013; Gomes et al., 2012) and benefits persist for at least 6–12 weeks after the end of the treatment (Mantovani et al., 2010a Hawken et al., 2016) and it appears to be more effective than the augmentation with antipsychotic drugs (Pallanti et al., 2016). Moreover, this protocol produces long-lasting changes of the synaptic activity while entailing a small probability of adverse effects (Kozyrev et al., 2018; Lefaucheur et al., 2020; Rossi et al., 2020).

So far, no study correlates the clinical benefits induced by TMS on OCD symptoms with rsFC patterns modifications. In the present pilot study, we treated 9 drug-resistant OCD patients with a novel, personalized, low frequency, and neuronavigated rTMS protocol targeting the subjects bilateral SMA. Aims of the study were: (i) to test the feasibility and safety of the approach (ii) to measure immediate and long-lasting symptomatology changes (iii) to verify correlations between rsFC modifications and clinical measures.

2. Methods

2.1. General procedure and participants

For this open-label rTMS study, nine OCD patients were recruited at the OCD clinic of the University Federico II Hospital of Naples. The subsequent procedures were carried out at the Siena Brain Investigation and Neuromodulation Lab (Si-BIN Lab) of the University of Siena. As shown in Fig. 1, the patients underwent two pre/post psychometric and MRIs assessments and 10 rTMS sessions in five days. The inclusion criteria were: age between 18 and 70 years; primary diagnosis of OCD according to DSM-5 criteria; baseline Yale–Brown Obsessive-Compulsive Scale (YBOCS; Moritz et al., 2002) score>16; disease lasting for at least the entire past year; failure to remit symptoms using conventional drug treatment (SRIs) and/or CBT during the past 6 months. The presence of contraindications to the application of TMS (risk of seizure, abuse of substances, presence of pacemaker or cochlear implants) was preliminarily investigated (Rossi et al., 2020). We also excluded patients who participated in previous TMS treatments and those taking drugs capable to significantly modify cortical excitability (atypical antipsychotics or benzodiazepines). rTMS was added to the ongoing medications (Table S1 on Supplemental Information).

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the protocol was approved by the Local Ethical Committee. Nine OCD right-handed patients (5 females; mean age: 44.43 years; SD: 11.10) were enrolled and signed the informed consent. One patient stopped the treatment after the first day, due to a subjective report of worsening of pre-existing depressive symptoms. Eight patients completed the study (4 females; mean age: 40.75 years; SD: 13.24).

2.2. MRI acquisition preprocessing

Each patient underwent a structural and functional MRI session before (T0) and after (T1) the rTMS intervention. Images were acquired with a Philips INTERA scanner. The whole-brain anatomical image (T1-weighted Fast Field Echo sequence; resolution: 1 mm^3) was obtained along AC-PC line (Repetition Time (TR) = 25 ms; Echo Time (TE) = 4.5; number of slices = 150; thickness gap = 1 mm; flip angle (FA) = 30). Functional images were acquired using a resting state fMRI (rs-fMRI) protocol (TR = 2500 ms; TE = 40.0; number of slices = 23; thickness

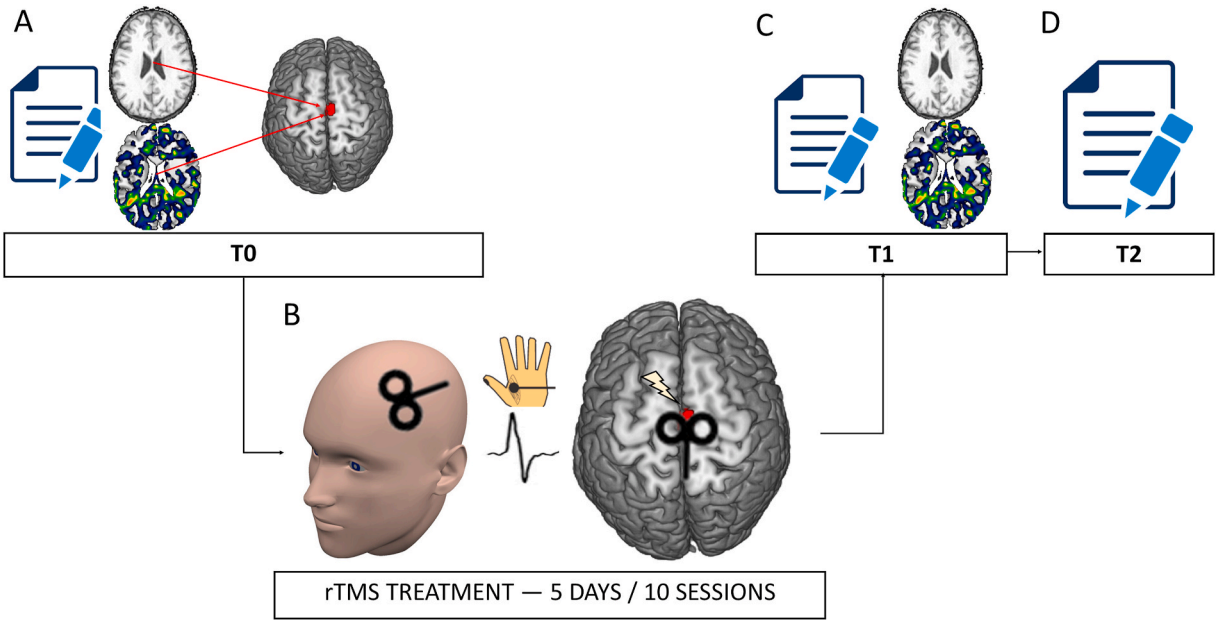

Fig. 1. Patients underwent the clinical assessment (YBOCS and CGI) and a scan session before the rTMS intervention. The stimulation site was identified using bilateral SMA activation analysis (**A**). The rTMS treatment lasted 5 days, with a double-daily stimulation. Before each session, the patients right and left RMT were measured. The 1 Hz rTMS was applied to the individualized bilateral SMA target (**B**). After the end of the last session, the patients underwent a YBOCS/CGI reassessment and a fMRI scanning session (**C**). After 3 months from the end of the treatment, patients were evaluated with CGI scale (**D**).

gap = 6.0; FA = 90). MRIs were preprocessed using SPM12 toolbox (Statistical-Parametric-Mapping; http://www.fil.ion.ucl.ac.uk/spm/) of MATLAB (MathWorks, MA, USA): the first three fMRI volumes were excluded to allow steady-state-magnetization (Miller et al., 2011). The EPI images were slice-timed following the interleaved descending acquisition order. Physiological head motion was removed through realigning and reslicing correction using an overall mean image from fMRI scan. Then, fMRI data were co-registered with the structural image, segmented and normalized to the Montreal Neurological Institute (MNI) template brain. The image was smoothed using an isotropic Gaussian kernel (full-width at half-maximum (FWHM) of 8 mm).

2.3. Stimulation site personalization

Brain networks modulation requires absolute precision and individual differences in rsFC must be taken into account (Fox et al., 2012; Santarnecchi et al., 2018). Thus, we conceptualized a novel individualized rTMS treatment, combining patient's anatomical image with intrinsic rsFC and identifying participant's SMA activation (Mantovani et al., 2010b) using CONN toolbox atlas (Whitfield-Gabireli & Nieto-Castanon, 2012; www.nitrc.org/projects/conn, RRID: SCR_009550). Then, the SMA BOLD signal threshold was adjusted using MRIcron software. Lastly, to assure a coherent intrasession and intersession stimulation (Fitzgerald et al., 2009; Cocchi and Zalesky, 2018), the individualized target hotspot was marked in subject's MRI loaded into our neuronavigation system (NetBrain9000 Neuronavigator–EBNEURO).

2.4. rTMS treatment and safety

Two daily sessions of rTMS, spaced at least 4 h for 5 consecutive days over one week were administered, in line with the last available safety guidelines (Rossi et al., submitted). The treatment was carried out by means of an STM9000 stimulation device and a 70-mm cooled figure- 8 focal coil (Ates-EBNeuro Ltd). Before each treatment, we measured the resting motor threshold (RMT) - defined as the intensity of the magnetic pulse to evoke a motor response of 50 μV in 5 out of 10 consecutive attempts when stimulating over the primary motor cortex (M1) (Rossi et al., 2009)- of both hemispheres. We registered muscular twitches bilaterally from the first dorsal interosseous (FDI) using a conventional electromyography (EMG) recording system. EMG activity was amplified, analogue band-pass filtered (3Hz–1 kHz), and digitized (A/D rate 5 kHz) by a micro 1401 unit and Signal 2 software (Cambridge Electronic Devices, Cambridge, UK). Then, the coil was positioned on the individualized SMA point and held tangentially along the sagittal midline to stimulate the SMA bilaterally. rTMS was delivered at an intensity of 110% of the lowest RMT (right or left), at a frequency of 1 Hz for 60 min for a total of 3600 per session and 7200/day total stimuli. During the session, patients seated in an armchair and wore earplugs. A series of potential side effect (headache, scalp pain, seizure, trouble concentrating, scalp burn, neck pain, memory impairment, hearing impairment, impaired cognition) were investigated before and after each rTMS session (Mantovani et al., 2010a).

2.5. Clinical assessments and analysis

In order to measure patients' obsessions and compulsions changes, YBOCS was administered before (T0) and after (T1) the treatment. Moreover, to measure eventual long-lasting effects of the treatment, the severity of the disorder was investigated using the Clinical Global Impression-Severity (CGI) rating scale at T0, T1 and three months after the end of the treatment (T2). Only subjects with a YBOCS score reduction ≥25% between T0 and T1 (Mantovani et al., 2010a) were classified as "responders".

Statistical analysis was carried out using SPSS v 16.0 (SPSS Inc., Chicago, IL, USA). Repeated measures analysis of variance (rm-ANOVA) with Time as within-subjects factor (2 levels: T0 and T1) was performed to evaluate the effects of the treatment on OCD core symptomatology assessed with YBOCS. To evaluate long-lasting effects on the general health of the patient, a rm-ANOVA was performed on the CGI score (three-level Time factor: T0, T1 and T2). Lastly, to verify relationship between questionnaires, we conducted a correlational analysis between YBOCS and CGI scores.

2.6. Power analysis calculation

An A-priori ANOVA for Repeated Measures (between factors) was performed using G-Power software (Faul et al., 2007), in order to calculate an appropriate sample size and achieve an optimal statistical power. Input parameters of the simulation were: 2 rTMS conditions (active rTMS and sham to the SMA); effect size f: 0.51 (Mantovani et al., 2010); alpha: 0.05; 1-beta error probability: 0.80.

2.7. Resting-state functional connectivity analysis

To analyse connectivity patterns modifications between MRIs assessments, the CONN toolboxwas used. We performed seed-based analysis with a threshold level of $p < .05$ uncorrected and a cluster-level threshold of $p < .05$ FDR corrected and bilateral SMA as seed region. The Harvard-Oxford (Desikan et al., 2006) and the thalamic nuclei atlas (Najdenovska et al., 2018) were used.

Aims were i) to investigate significant rsFC changes between the target area and the rest of the brain, performing a bivariate correlation and contrasting fMRI-T1>fMRI-T0; ii) to test the impact of baseline YBOCS scores on rsFC changes. Thus, we conducted two regression analyses contrasting fMRI-T1>fMRI-T0 including YBOCS-T0 and YBOCS-T1 as second level covariates of interest.

3. Results

3.1. Safety and clinical outcomes

After rTMS applications, transient mild side effects were reported (headache, neck pain) in all patients. No severe adverse effects related to TMS, no seizures and no transient cognitive/neurological impairments were observed or reported from the subjects. Immediately after rTMS treatment, patients showed a significant decrease of OCD symptoms (Fig. 2).

Individual scores are reported on Table 1. The reduction of the YBOCS total score over Time was significant ($F(1,7) = 16.162$; $p = .005$), as well as the reduction of obsessions ($F(1,7) = 14.147$; $p = .007$) and compulsions ($F(1,7) = 12.290$, $p = .010$). CGI scores analysis revealed a significant main effect of Time ($F(1,7) = 37.333$, $p < .05$ at T1 ($p = .010$) and at T2 ($p = .001$) compared to baseline (no differences between T1 and T2). Moreover, we found a high correlation between YBOCS score and CGI scores at T1 ($r = 0.084$, $p = .008$).

YBOCS-T1 score decreased in all patients compared to YBOCS-T0. Four patients were classified as "responders" (i.e., more 25% reduction of the total score; symbol: ◯ in Table 1) and four as "non-responders" (symbol: ● in Table 1). However, 2 non-responders (participants n.4 and n.7; symbol: * in table n.1) reported an improvement of their general health condition during the follow-up, as confirmed by the reduction of their CGI-T2 severity score (25% score change between timepoints).

3.2. Power analysis

A-priori ANOVA showed that a total sample of 20 participants are required to achieve a statistical power of .80 and discriminate significant differences between different conditions (Noncentrality parameter λ: 8.91; Critical F: 4.41; degrees of freedom: 1,18).

3.3. rsFC modifications

After the rTMS intervention, bilateral SMA decreased its connectivity with a number of subcortical and cerebellum regions, unilaterally or

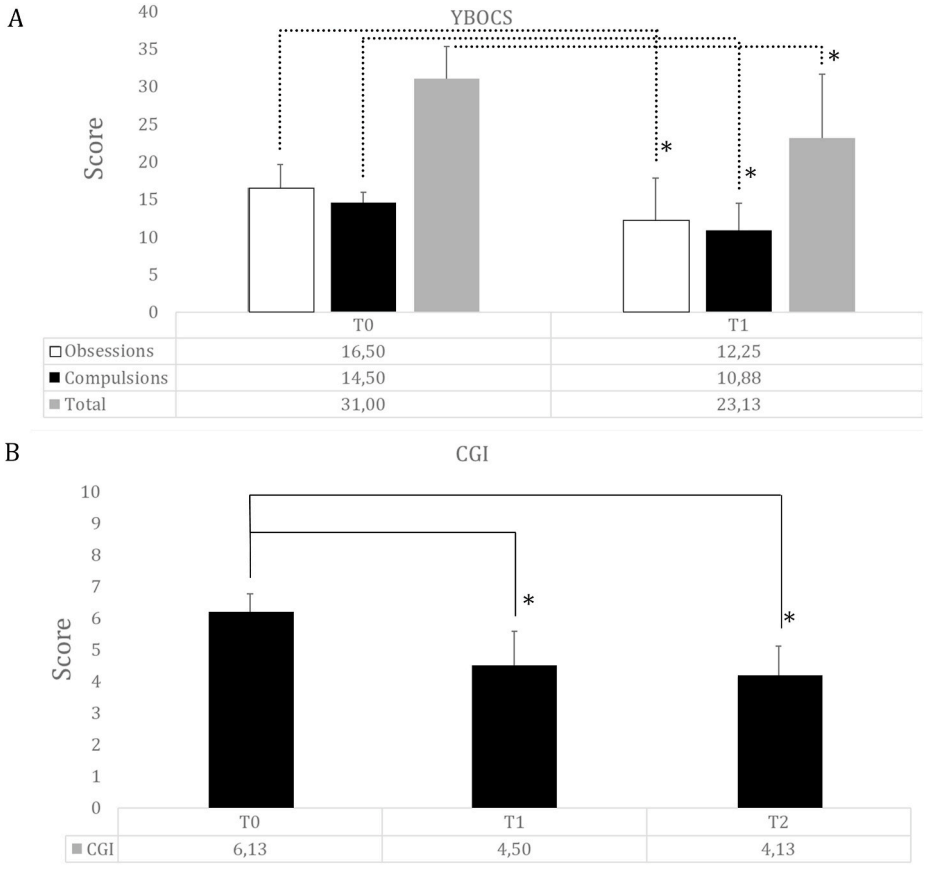

Fig. 2. Clinical measures of YBOCS (**A**) and CGI (**B**) across three timepoints: before (T0), immediately after (T1) and three months from the end of the rTMS treatment (T2). *: significant difference between scores.

Table 1
Demographic characteristics of the patients and clinical measures of compulsions and obsessions symptoms assessed with YBOCS at T0 and T1; CGI score across timepoints: before (T0), after (T1) and three months after the intervention (T2). Patients were classified as "responders" (◯) or "non-responders" (●) (see Methods for criteria), Patients with a significant CGI long-lasting effect are also reported (*).

Patient	Sex	Age	YBOCS-T0			YBOCS-T1			CGI-T0	CGI-T1	CGI-T2
			Obses.	Comp.	Total	Obses.	Comp.	Total	Score	Score	Score
1 (◯)	M	30	14	14	28	9	7	16	5	4	4
2 (◯*)	F	24	15	14	29	12	9	21	6	4	3
3 (●)	F	24	21	15	36	20	12	32	7	6	6
4 (●*)	M	52	13	12	25	10	10	20	6	5	4
5 (◯*)	F	49	15	15	30	7	12	19	7	4	4
6 (●)	M	59	21	17	38	19	18	37	6	6	5
7 (●*)	F	43	18	14	32	16	12	28	6	4	3
8 (◯*)	M	45	15	15	30	5	7	12	6	3	4
MEAN		**40,75**	**16,50**	**14,50**	**31,00**	**12,25**	**10,88**	**23,13**	**6,13**	**4,50**	**4,13**
S.D.		**13,24**	**3,12**	**1,41**	**4,24**	**5,55**	**3,56**	**8,46**	**0,64**	**1,07**	**0,99**

bilaterally (t (7) = -20.14; p-uncorrected <.05; k = 1796; +24,-34,-06): more specifically, with bilateral putamen, right caudate, right globus pallidus (pars externa), brain stem, hippocampus, parahippocampal gyrus, right cerebellum (parts 3, 9, 45 vermis 3 and vermis 9), bilateral pulvinar, right anterior, right ventral-latero-ventral, right ventral-anterior, ventral-latero-dorsal parts of thalamus (Fig. 3).

A higher YBOCS-T0 score predicted an increased rsFC between SMA and basal ganglia/fronto-temporal regions (t (7) = 18.61; p-uncorrected<.05; k = 1669; −14,+26,+12). Specifically, we detected a higher rsFC with bilateral fronto-orbital cortex, left temporal pole, anterior cingulate cortex, insular cortex, subcallosal cortex, and caudate, putamen, NAc bilaterally (Fig. 4).

Higher YBOCS-T1score correlated with a greater rsFC between bilateral SMA and prefrontal/subcortical areas (t (7) = 9.28; p-uncorrected<.05; k = 1998; −02,+00,-18) in putamen, caudate, insular cortex and nucleus accumbens (NAc) bilaterally, left pallidus (pars externa and interna), anterior cingulate cortex, temporal pole, bilateral fronto-orbital cortex (Fig. 5). Moreover, higher YBOCS-T1 score correlated with a decreased rsFC pattern between bilateral SMA and right frontal cortex (t (7) = -7.15; p-uncorrected<.05; k = 1669; +38,+36,+24) in frontal pole, superior frontal gyrus and middle frontal gyrus. Lastly, we found a decreased connectivity between bilateral SMA and right temporo-parietal cortex (t (7) = -5.56; p-uncorrected<.05; k = 1180; +58,-22,+06).

Lastly, as shown in Fig. 6, YBOCS-T0 and YBOCS-T1 scores resulted significant predictors of rsFC changes detected during fMRI-T1 (R^2 = 0.98; beta = 0.03; T (6) = 18.61; p = .000001; R^2 = 0.94; beta = 0.014; t (6) = 9.63; p = .000036 respectively).

4. Discussion

This open-label study introduced a double-daily rTMS application,

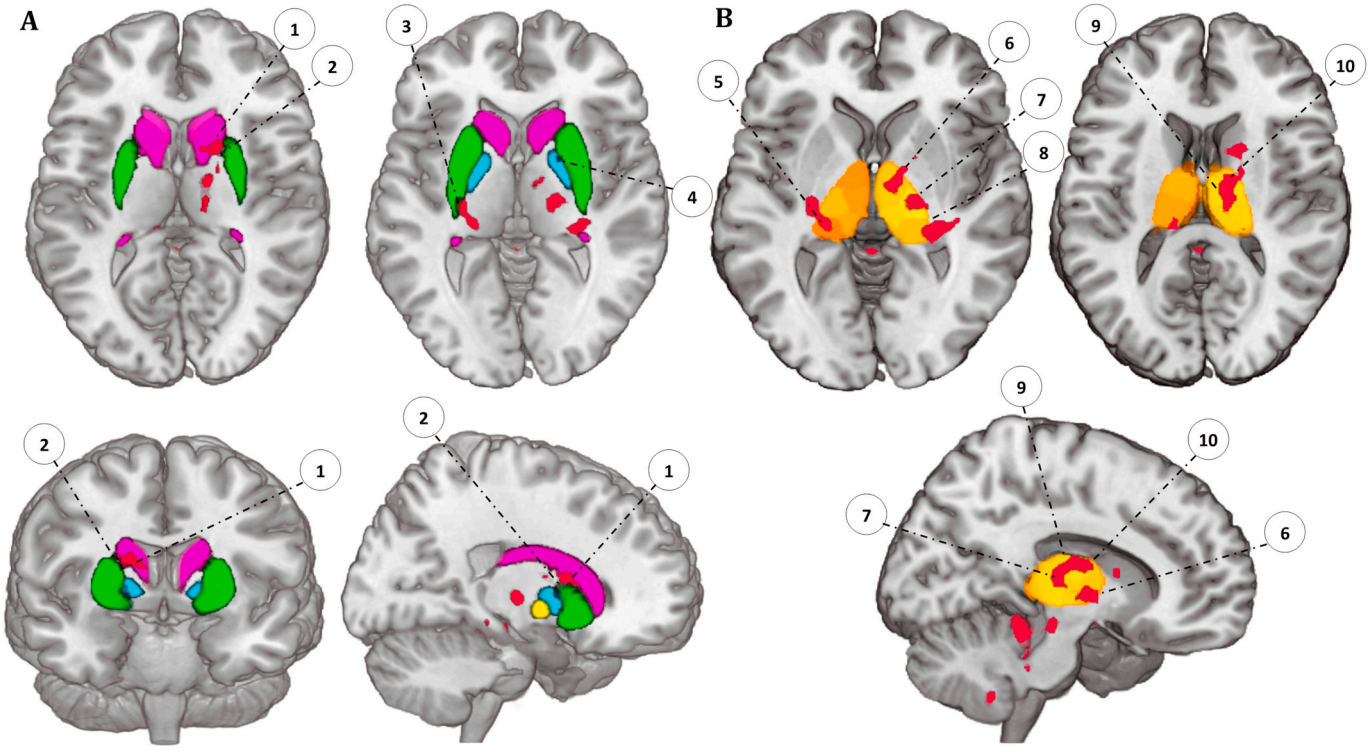

Fig. 3. Seed-based analysis connectivity maps (Seed: bilateral SMA). Contrast T1> T0 - RED: decreased connectivity between seed and the rest of the brain is represented. The SMA decreased its connectivity with the basal ganglia and in particular with right caudate (1), right putamen (2), left putamen (3), right globus pallidus (pars externa) (4) (**A**) and with thalamus specifically with left pulvinar (5), right anterior nucleus (6), right ventral-latero-ventral nucleus (7) right pulvinar (8), right ventral-latero-dorsal nucleus (9), right anterior ventral nucleus (10) (**B**). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

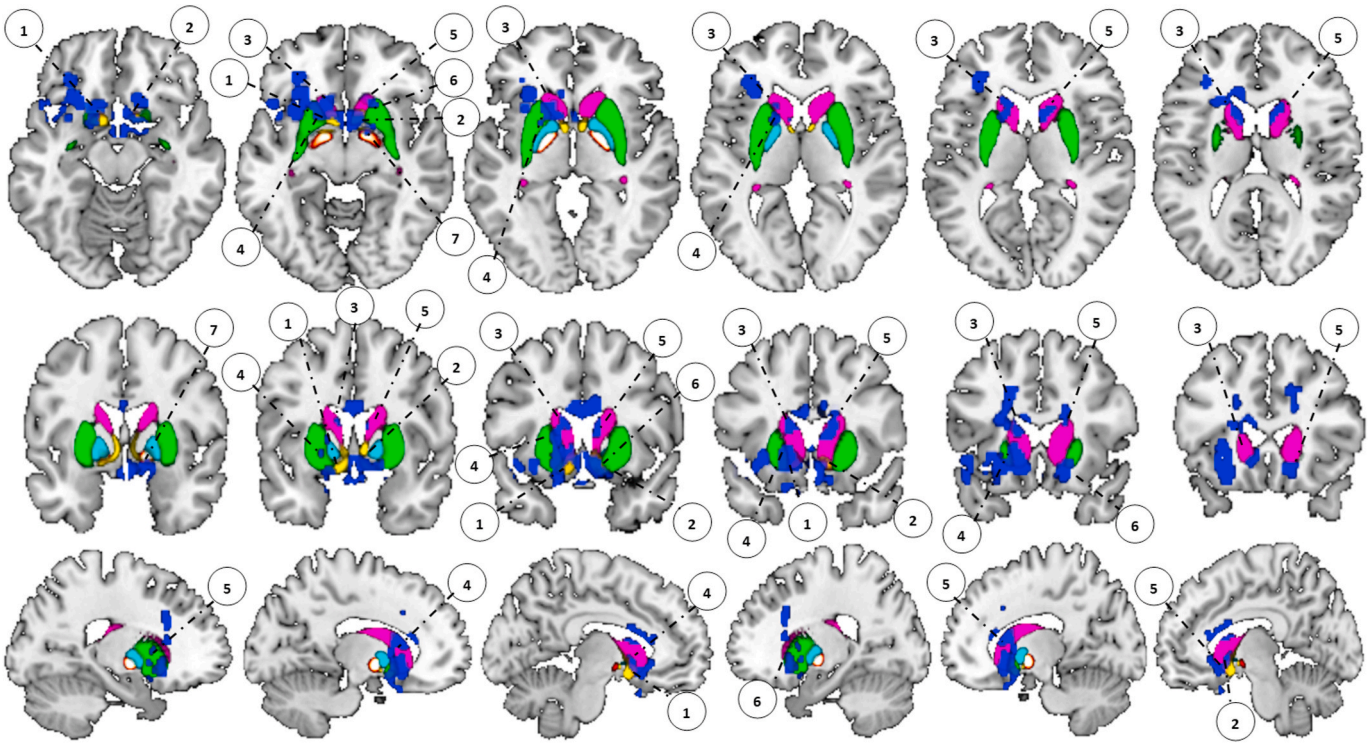

Fig. 4. Regression analysis rsFC maps. Contrast fMRI-T1>fMRI-T0 - BLUE: increased connectivity. Higher YBOCS-T0 score predicts a higher connectivity between bilateral SMA with dorsal and ventral striatum in the left NAc (1), right NAc (2), the left caudate (3), left putamen (4), right caudate (5), and right putamen (6). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

personalized on the basis of individual SMA hyperactivity, in treatment-resistant OCD patients. The set-up was based on previous trials outcomes (Mantovani et al., 2005, 2010a, 2013; Gomes et al., 2012; Hawken et al., 2016; Carmi et al., 2019) and optimized to improve the benefits/costs ratio (i.e., shorter treatment course) in order to obtain clinical responses, without side effects. The protocol resulted feasible and safe: none of the patients reported significant side effects related to rTMS, apart the usual mild and transient headache not requiring pharmacological treatment (Rossi et al., 2009).

The clinical outcomes confirmed that low-frequency rTMS on SMA is an effective treatment for OCD (Rehn et al., 2018; Carmi et al., 2019; Rapinesi et al., 2019). At YBOCS-T1 assessment, patients reported a significant reduction of symptoms, in both obsessions and compulsions. Compared to baseline, the total YBOCS score decreased by 25,4%; obsessions and compulsions dropped by 25,8% and 25,5% respectively. A similar outcome was found in previous studies based on longer rTMS treatment course (i.e., from 2 to 8 weeks) (Gomes et al., 2012; Hawken et al., 2016; Mantovani et al., 2006, 2010a, 2013), but as far as we know, this is the first evidence from a double-daily one-week rTMS treatment targeting the SMA. Three months after the end of the treatment, we still observed a significant decrease of patients' disorder severity, thus confirming a long-term clinical benefit of the stimulation (Hawken et al., 2016; Mantovani et al., 2005; 2010a; Seo et al., 2016).

YBOCS-T1 score decreased more than 25% in 50% of participants; however, rTMS long-lasting effect, based on the CGI score, showed that only two participants remained markedly or severely ill in the follow-up (Busner and Targum, 2007). These two subjects had the highest YBOCS-T0 scores (n.3/n.6 in Table 1) and were categorized as patients with a very severe disease (Storch et al., 2015); their outcome confirmed that rTMS might not be efficacious in patients with extreme symptoms (Kang et al., 2009) and suggest that the severity of the disorder might be taken into account during the screening session and considered as a further exclusion criterion.

Now, it is known that rTMS neuromodulatory effect may be strongly influenced by the connectivity patterns of the target brain area with specific regions of the brain (Castrillon et al., 2020); in fact, we effectively observed a decrease of rsFC between the bilateral SMA with basal ganglia, thalamus and cerebellum (Fig. 3), i.e. brain regions belonging to the CSTC circuits and strongly functionally connected.

After rTMS, the bilateral SMA decreased its rsFC pattern with the right caudate, the right globus pallidus and the putamen bilaterally. Likewise, a decreased metabolism of the caudate was found after drug treatment with paroxetine in OCD (Hansen et al., 2002). During a planning task, left putamen and right caudate showed a greater activation in OCD patients than controls, and the results were connected to the difficulty in task execution. Moreover, using a symptom provocation paradigm during fMRI, an abnormal activation of the right caudate was observed in OCD patients thinking of ritually washing their hands, while a significant activation in the globus pallidus and the putamen was observed during an imagination of checking (Mataix-Cols et al., 2004). Therefore, successful treatments for OCD seems to be linked to a normalization of hyperactive basal ganglia.

Furthermore, specific regions of the thalamus, including bilateral pulvinar, right nucleus, right ventrolateral/anteroventral parts appear to have a decreased connectivity after rTMS. In recent neuroimaging studies, shape abnormalities in the anterior, lateral and pulvinar nuclei have been highlighted in OCD (Kang et al., 2009; Shaw et al., 2015). Moreover, the pulvinar is involved in attentional processing and its lesions or abnormalities lead to an impairment of attentional resources in OCD (Snow et al., 2009; Ivanov et al., 2010). rsFC changes between bilateral SMA and cerebellar regions were probably elicited by the strong functional connection between the CSTC circuit and cerebellum to speculate a revalidation of the CSTC model, including specific cerebellar areas (Kim, 2015). Moreover, cerebellar involvement has been taken into account recently in OCD, with several morphovolumetric and functional connectivity differences between patients and healthy controls (Kasikci et al., 2015).

Interestingly, the rsFC pattern modifications that we found after

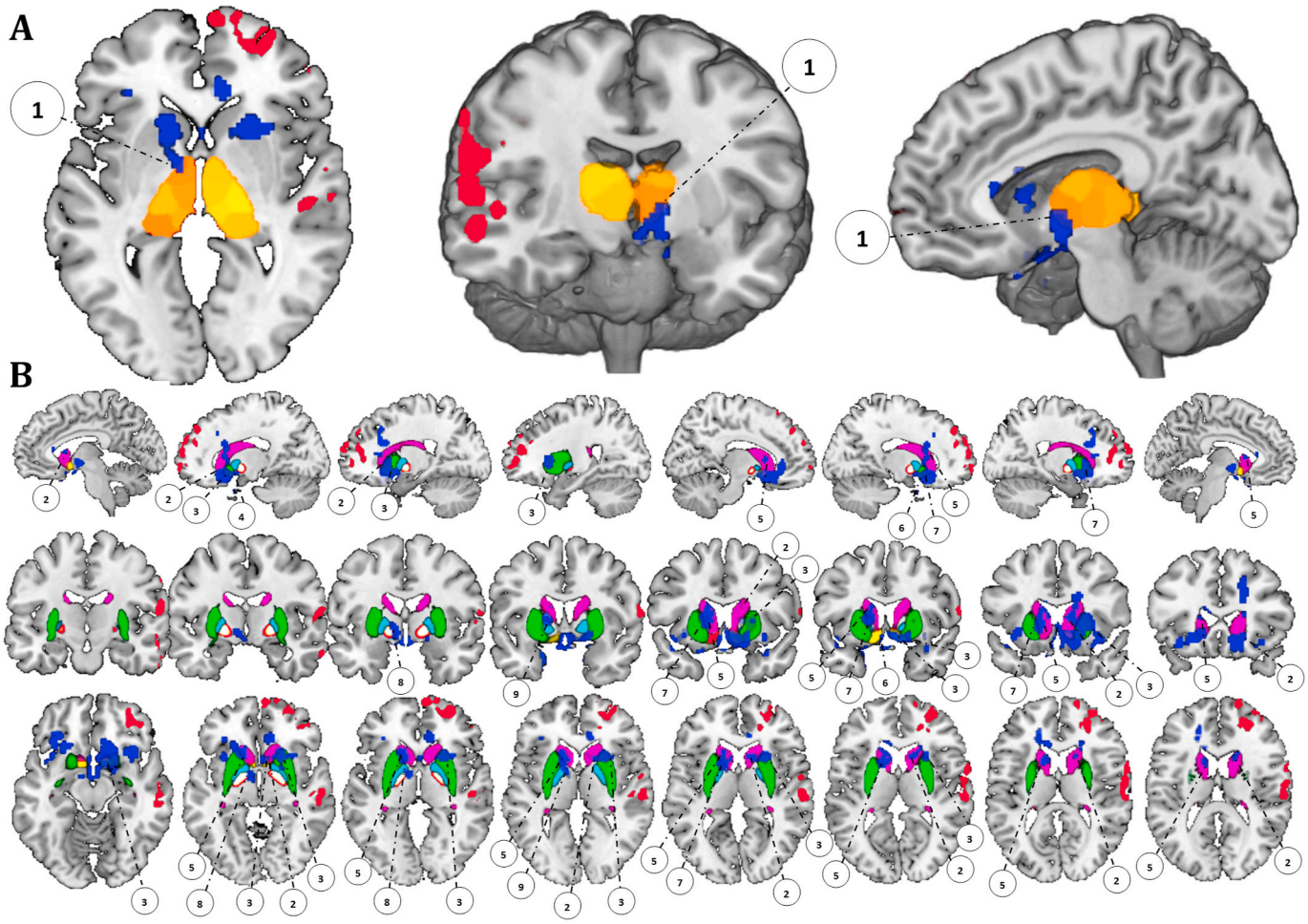

Fig. 5. Regression analysis rsFC maps. Contrast fMRI-T1>fMRI-T0 - RED: decreased connectivity; BLUE: increased connectivity. SMA increases its connectivity with the thalamus and in particular with left ventral anterior nucleus (1) (**A**) and with basal ganglia in the right caudate (2), right putamen (3), right NAc (4), left caudate (5) left NAc (6), left putamen (7) left globus pallidus (pars interna) (8), left globus pallidus (pars externa) (9) (**B**). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

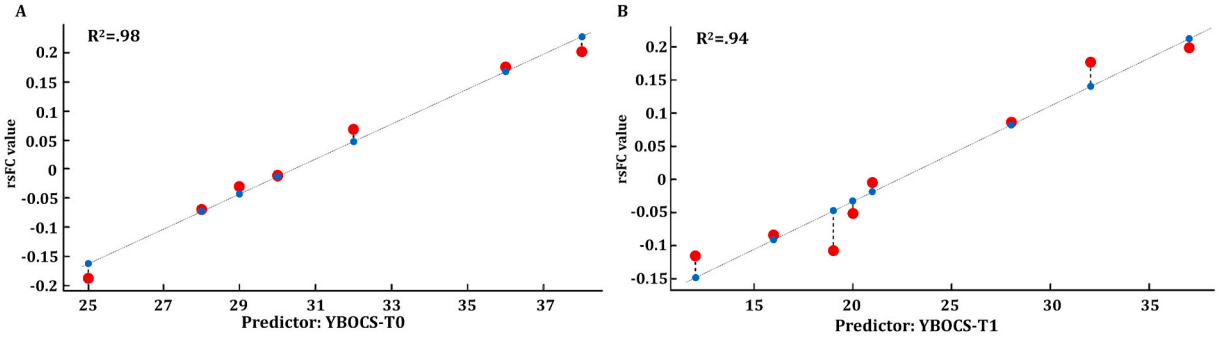

Fig. 6. Regression analysis scatter plots: rsFC value between SMA and subcortical regions detected during fMRI-T1. The connectivity pattern is significantly predicted by YBOCS-T0 **(A)** and YBOCS-T1 **(B)** scores.

rTMS are similar to neuroimaging findings of functional connectivity changes after a successful drug or CBT treatment in OCD patients (Atmaca, 2013; Freyer et al., 2011; Lázaro et al., 2008). Thus, our outcome reinforces the theory of a higher activity within CSTC circuitry as the neural basis of OCD, especially in its direct loop (Lusicic et al., 2018; Rapinesi et al., 2019) and that inhibitory rTMS targeting SMA has the capability to normalize the cortical-subcortical abnormal hyperactivity (Strafella et al., 2001; Saba et al., 2015; Lusicic et al., 2018), restoring a more physiological level of the functional communication within the CSTC direct loop. Changes in rsFC have been probably facilitated by the strong anatomic and functional interactions between SMA and subcortical regions (Ruan et al., 2018), confirming that rTMS might have a direct effect on the stimulated cortical structure and an indirect synapse rearrangement rebound on connected deep brain structures (Strafella et al., 2001).

Correlations between neurophysiological measures and treatment response might help to predict which patientsare more likely to improve symptomatology after rTMS. For instance, rTMS-induced clinical

improvement, measured by YBOCS and CGI, inversely correlated with baseline resting motor threshold (RMT) (Mantovani et al., 2010a) and with an increase in short-interval intracortical inhibition (SICI) (Mantovani et al., 2013) a measure of GABAergic intracortical activity (Kang et al., 2007); therefore, monitoring these neurophysiological measures during rTMS might be useful to predict its clinical effect.

To provide further predictors of therTMS treatment success, we investigated correlations between the YBOCS scores and the rsFC modifications, merging the clinical with the fMRI data and the regression analysis results provided newsworthy elements to discuss. Indeed, higher YBOCS-T0 and YBOCS-T1 scores predicted the fMRI-T1 rsFC changes between bilateral SMA and basal ganglia nuclei; in particular, we detected connectivity modifications between the bilateral striatum (NAc, putamen and caudate) and globus pallidus. Basal ganglia play a central role in the CSTC motor pathway and motor learning abilities, controlling sensory information processes and promoting/antagonizing a motor output (Groenewegen, 2003). The altered activation in the striatum was detected in OCD patients (Saxena et al., 2004), probably linked to excitatory projections that come from the SMA regions (Del Casale et al., 2011). Indeed, a low performance at serial reaction time task (SRTT) has been highlighted in patients with Parkinson's or Huntington's disease, having primarily motor dysfunctions and consistent with CSTC loops damage (Knopman and Nissen, 1991); a lower performance in the same task is detectable in patients with OCD compared to healthy controls (Rauch et al., 2007).

We found that the two aforementioned OCD patients who did not receive clinical benefits from rTMS (n.3/n.6 in Table 1) are those with the highest rsFC values detected at fMRI-T1 with the regression analysis (see Fig. 6). Taking all into account, the clinical severity and the CSTC connectivity patterns of OCD patients seem to be strongly connected and, apparently, the most severe patients were those who might not benefit from rTMS. This could probably be due to the persistence, in these patients, of the CSTC hyperactivity, particularly in basal ganglia, even after the rTMS treatment.

Results of this pilot investigation are in agreement with two previous studies who failed to prove any efficacy of SMA rTMS in OCD patients with a severe symptomatology (Kang et al., 2009; Pelissolo et al., 2016). We speculate that patient's baseline YBOCS score of 30 might be considered the clinical threshold for the application of rTMS in OCD, since a higher YBOCS score indicates an extremely severe disease state (Storch et al., 2015) that might require a different and more aggressive neuromodulatory treatment strategy, such as deep brain stimulation (Carmi et al., 2019) or even electroconvulsive therapy (D'Urso et al., 2012).

4.1. Limitations, recommendations and future directions

The main limitation of the study is the small sample size. We are planning to expand our investigation on a larger sample of OCD patients to test fMRI connectivity outcomes and cerebral blood flow (CBF) changes using arterial spin labeling (ASL) scan. This functional investigation has the potential to test global and regional blood perfusion differences following a non-invasive neuromodulatory treatment (Mesquita et al., 2013).

A second limitation is the open-label design. We partially controlled for that bias by assigning the clinical assessments and the treatment to different investigators. Moreover, the raters at T0, T1 and T2 were not aware of the actual study timepoint.

Third, as the trial is not controlled with a sham rTMS, a placebo response cannot be ruled out, although evidence indicates that OCD patients have low sham-treatment effects (Huppert et al., 2004).

The feasibility of the innovative rTMS protocol has been verified and the next step is to carry out a sham-controlled trial in order to test definitively whether our new protocol is clinically effective (Whitehead et al., 2016). Thus, we have calculated that a sample of 20 subjects will be needed to have a statistical power of 0.8 (Faul et al., 2007).

5. Conclusion

The present study provides the first evidence of the safety and feasibility of a novel double-daily individualized rTMS treatment delivered to the SMA of OCD patients. This 5-day protocol produced an acute and long-lasting clinical improvement in patients with treatment-resistant OCD and it significantly changed the brain connectivity patterns in the CSTC circuits associated with the symptoms.

Author contributions

AMa and SR conceptualized and designed the study protocol. GD enrolled the patients. FN, DM, GS, ET, AMe, GD, AMa, LM collected the data. FN performed statistical analysis. SM, AMa, GD, ES oversaw study conduction. FN and AMa edited the first draft. All authors critically reviewed the manuscript for content and approve the final version for publication.

Financial disclosures

All authors report no conflict of interest.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgements

The authors warmly thank dr. Elena Toscano and dr. Sara Patti for their precious help in the enrollment process and in data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.10.030.

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