Functional connectivity changes and symptoms improvement after personalized, double-daily dosing, repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder

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INTRODUCTION

Obsessive compulsive disorder (OCD) is a disabling psychiatric condition consisting of a heterogeneous combination of intrusive thoughts, repetitive behaviors or mental acts. These characteristics are associated to aberrant resting state functional connectivity (rsFC) patterns within the cortico-striatal-thalamo-cortical (CSTC) circuits, including 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). 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, reducing OCD symptoms (Mantovani et al., 2006) and benefits persist for at least 6-12 weeks after the end of the treatment (Mantovani et al., 2010). However 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.

METHODS

A novel protocol of 1-week MRI-guided individualized double-daily sessions of rTMS treatment (1-Hz; 110% of resting Motor Threshold, 7,200 pulses/day) has been applied. The study design is shown in **Figure 1**. Because the brain networks modulation requires absolute precision and individual differences in rsFC must be taken into account (Santarnecchi et al., 2018), we conceptualized a novel individualized rTMS treatment, combining patient's anatomical image with intrinsic rsFC and identifying participant's SMA activation (Mantovani et al., 2010). 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).

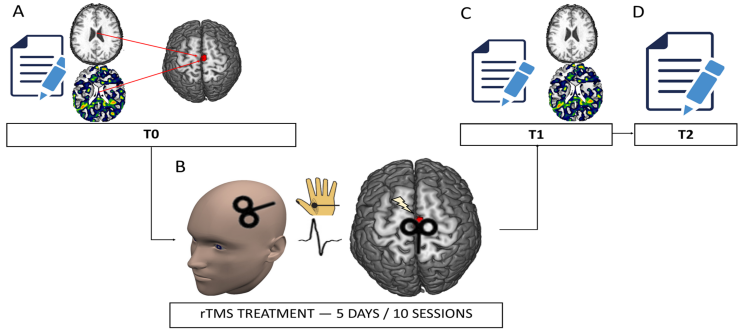


Figure 1. Study design. Clinical assessment (YBOCS and CGI) and a scan session has been performed before the rTMS intervention. The stimulation site was identified and personalized using bilateral SMA activation analysis (A). The rTMS treatment lasted 5 days, with a double-daily stimulation. Before each session, the right and left RMT were measured. 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 assessment and a fMRI scanning session (C). After 3 months from the end of the treatment, patients were evaluated with CGI scale (D).

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. In addition, 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). Moreover, to investigate significant rsFC changes between the target area and the rest of the brain, we performed a bivariate correlation contrasting fMRI-T1>fMRI-T0. Lastly, to test the impact of baseline YBOCS scores on rsFC changes, we conducted two regression analyses contrasting fMRI-T1>fMRI-T0 including YBOCS-T0 and YBOCS-T1 as second level covariates of interest.

RESULTS

Patients reported no side effects during and after rTMS. Personalized rTMS treatment led to a significant improvement of OCD symptoms measured by YBOCS (average 25%; $F_{1,7}$=16.162; p=.005) and persistence of benefit up to 3-months follow-up measured by CGI ($F_{1,7}$=37.333, p<.05, **Figure 2**). RsFC analysis revealed a significant reduction of connectivity patterns between bilateral SMA and subcortical regions, specifically in the basal ganglia and thalamus (t(7)=-20.14; p-uncorrected <.05; **Figure 3**). Additional analysis showed that OCD symptoms severity correlates with a higher connectivity pattern between bilateral SMA and subcortical regions (t(7)=18.61; p-uncorrected <.05; **Figure 4A**). Moreover, the regression analysis revealed that higher YBOCS-T1 score correlated with a greater rsFC between bilateral SMA and prefrontal/subcortical areas (t(7)=9.28; p-uncorrected <.05) in putamen, caudate, insular cortex and nucleus accumbens (NAc) bilaterally, left pallidus (external and internal pars), anterior cingulate cortex, temporal pole, bilateral fronto-orbital cortex (**Figure 4B**).

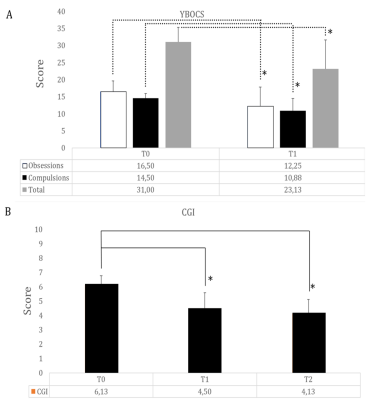


Figure 2. Clinical measures of YBOCS (A) and CGI (B) across three timepoints: before (T0), immediately after (T1) and three months from the end of the rTMS treatment (T2). *: significant difference between scores.

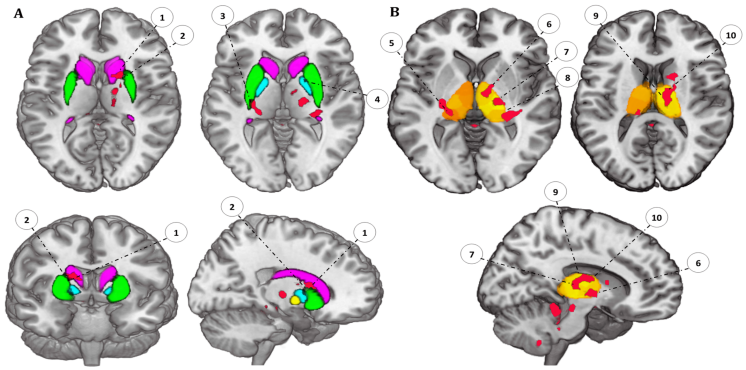
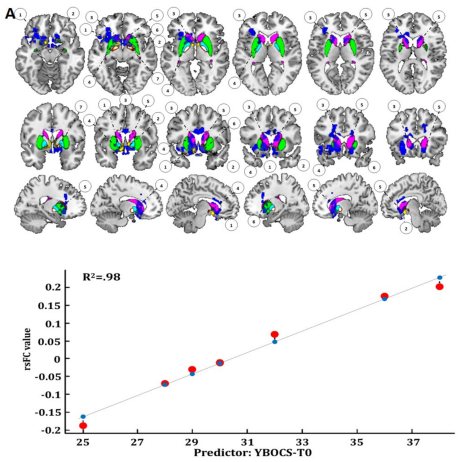


Figure 3. Seed-based analysis connectivity maps (Seed: bilateral SMA). Contrast T1> T0 - Decreased connectivity between seed and the rest of the brain is reported in red. SMA decreased its connectivity with right caudate (1), right putamen (2), left putamen (3), right globus pallidus (pars externa)(4) (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).



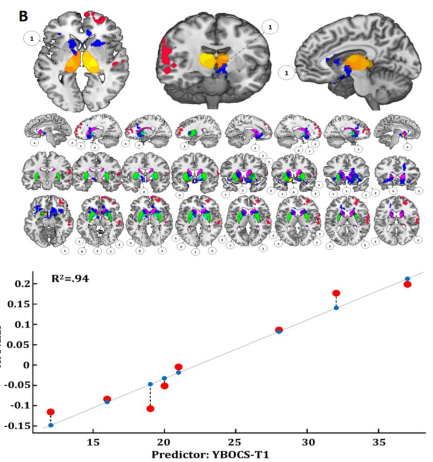


Figure 4. Regression analysis rsFC maps. Contrast fMRI-T1>fMRI-T0 - **Panel A** shows that higher YBOCS-T0 score predicts an higher connectivity between bilateral SMA and left NAc (1), right NAc (2), left caudate (3), left putamen (4), right caudate (5), and right putamen (6) (connectivity increase in blue). **Panel B** shows that higher YBOCS-T1 score predicts an higher connectivity between SMA and the left ventral anterior nucleus of the thalamus (1), the right caudate (2), right putamen (3), right NAc (4), left caudate (5) left NAc (6), left putamen (7) left globus pallidus (internal (8) and external (9) pars) (connectivity increase in blue, connectivity decrease in red). The scatter plots indicate the rsFC values between SMA and subcortical regions detected during fMRI-T1 and shows thata the connectivity pattern is significantly predicted by YBOCS-T0 **(A)** and YBOCS-T1 **(B)** scores.

CONCLUSION

This open-label study introduced a double-daily rTMS application, personalized on the basis of individual SMA hyperactivity, in treatment-resistant OCD patients, providing the first evidence of the safety and feasibility of this new protocol. Moreover, the clinical outcomes confirmed that low-frequency rTMS on SMA is an effective treatment for OCD: this treatment 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.

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