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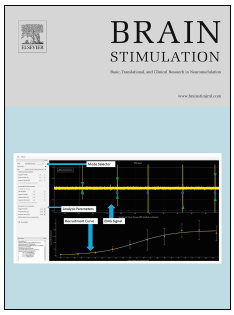

Neural correlates of successful orbitofrontal 1 Hz rTMS following unsuccessful dorsolateral and dorsomedial prefrontal rTMS in major depression: A case report

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Neural correlates of successful orbitofrontal 1 Hz rTMS following unsuccessful dorsolateral and dorsomedial prefrontal rTMS in major depression: a case report

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Letter to the Editor

Dear Editor –

Conventional rTMS protocols in major depressive disorder(MDD) target the left/right dorsolateral prefrontal cortex (DLPFC)[1,2], or occasionally the dorsomedial prefrontal cortex (DMPFC)[3]. However, response distributions are bimodal[4], with a subpopulation of nonresponders who appear to have distinctive symptoms such as anhedonia, and distinctive patterns of network activity in the frontal lobes[5]. Such individuals may therefore require alternative stimulation targets and protocols.

Recent large-N studies in MDD suggest overactivity/hyperconnectivity of a 'non-reward' circuit centered on the right lateral orbitofrontal cortex(OFC)[6]. This region is active during negative reinforcement or emotional reappraisal; the proposed 'non-reward attractor theory of depression' suggests that persistent self-sustaining activity in this OFC-centred circuit may perpetuate MDD symptoms[7]. Notably, 1 Hz right OFC-rTMS has shown efficacy in a crossover study in obsessive-compulsive disorder(OCD), also characterized by self-perpetuating negative affect and cognition[8]. However, OFC-rTMS has not previously been studied in MDD.

Here we report the case of an MDD patient who failed to respond to both DLPFC- and DMPFC-rTMS, but then showed marked improvement after 1 Hz right OFC-rTMS. We

also report functional MRI (fMRI) findings in this patient before and after the successful intervention.

Case Description

A 32-year-old female student with an 8-year history of medication-resistant MDD and generalized anxiety disorder (GAD) was referred for rTMS. GAD symptoms were unremitted since adolescence, while MDD symptoms featured prominent, chronic anhedonia. There was no history of OCD symptoms, hypomania or mania, delusions or hallucinations, substance misuse, and no history of self-harm or inpatient care. Medication history included unsuccessful trials of therapeutic doses of duloxetine, bupropion, T3, and a 5-session course of CBT abandoned for nonresponse. Past medical history was unremarkable, with no MRI/rTMS contraindications. Family history was unclear due to adoption. Medications at intake included bupropion XL 150 mg/300 mg alternate days, clonazepam 0.5 mg daily and zopiclone 7.5 mg nightly as-needed.

Course of Treatment

She underwent an initial course of 30 sessions of left DLPFC-rTMS, 5 sessions/week, 3000 pulses/session, 10 Hz, 120% resting motor threshold(RMT), 4 s on/26 s off, per conventional protocol[1,2], on a MagPro R30 device with a Cool-B70 coil under MRI-neuronavigation to MNI X-38 Y+44 Z+26. There was no improvement from 1 week pre- to post-treatment, either subjectively or on clinician-rated scales: 17-item Hamilton

Rating Scale for Depression (HRSD17) score 21 to 25; 30-item Inventory of Depressive Symptoms (IDS30) score 38 to 40.

She next underwent a course of 20 sessions of bilateral DMPFC-rTMS (procedure per[3]), 5 sessions/week, 1500 pulses/hemisphere/session, 20 Hz, 120% lower extremity RMT, 2.5 s on/10 s off, on a Cool-DB80 coil. Again there was minimal subjective improvement from 1 week pre- to post-treatment, and divergent outcomes on clinician-rated scales: $HRSD_{17}$ score 18 to 13; IDS_{30} score 26 to 39.

The patient declined electroconvulsive therapy or further medication trials, instead requesting additional rTMS. She then underwent a course of 30 sessions of right OFC-rTMS (positioning per[8]), 5 days/week, Cool-DB80 coil positioned over the Fp2 EEG site, handle vertical and upwards, 360 pulses/session, 1 Hz, 6 x 60 s trains, 30 s interval, as previously employed in a large multicentre trial of right DLPFC-rTMS[9]. This protocol was well-tolerated, with transient localized discomfort as the only adverse event. After OFC-rTMS, she reported marked improvement in mood and particularly in anxiety symptoms, with increased interest and pleasure in daily activities, noticeable to others, including her counsellor. She described it as “the most improvement that I’ve had on anything”. Clinical scores improved from 13 to 7 on the $HRSD_{17}$ and from 39 to 19 on the IDS_{30}. Item 21 of the IDS_{30} (pleasure/enjoyment of activities) improved from 2 (‘rarely derives pleasure from any activities’) to 0 (‘participates in and derives usual sense of enjoyment from pleasurable activities’). Her score on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) improved from 38 to 51. She

received twice-weekly maintenance sessions of OFC-rTMS for 6 weeks; at 3 months, her score on the $HamD_{17}$ had further decreased to 6, with full remission reported from mood and anxiety symptoms.

Neuroimaging

Resting-state functional MRI was acquired 1 week before and after OFC-rTMS (protocol per[10]) and preprocessed using FSL-based software modules, including 24-parameter motion correction, aCompCor correction for CSF/white-matter noise sources, bandpass filtering from 0.01-0.1 Hz, and FLIRT linear transformation to MNI-152 standard space. Seed-based correlation analyses were performed using a predefined set of atlas-defined nodes of the reward circuitry as ROIs (i.e., bilateral nucleus accumbens (NAcc), bilateral mediodorsal thalamus defined per Harvard-Oxford/Oxford Thalamic atlases and ventral tegmental area [MNI X-4 Y-15 Z-9]). We observed significant changes in functional connectivity throughout the predefined reward-network ROI set above, including decreased connectivity between the region underlying the sight of stimulation (right OFC; [MNI X+34 Y+36 Z-12]) and the bilateral NAcc. In addition, decreases in connectivity throughout the nodes of the OFC cortico-striatal-thalamo-cortical circuit were apparent (Fig. 1).

Discussion

Although 1 Hz right OFC-rTMS has been studied in OCD[8], this is the first report of OFC-rTMS used successfully in MDD without OCD. Despite failure to achieve remission with standard DLPFC- and DMPFC-rTMS protocols, the patient achieved marked improvements in mood, anxiety, and anhedonia with OFC-rTMS, with no tolerability issues arising.

fMRI revealed reductions in functional connectivity from OFC to nACC and other nodes of the orbitofrontal cortico-striato-thalamo-cortical loop circuit – a reciprocal finding to the increases in cortico-striato-thalamo-cortical connectivity through DMPFC seen with excitatory DMPFC-rTMS in MDD[10] and consistent with PET studies revealing reduced OFC metabolism following 1 Hz OFC-rTMS[8]. These findings are compatible with the interpretation that 1 Hz right OFC-rTMS may disrupt hyperactivity of a right OFC non-reward circuit, as in the 'non-reward attractor theory of depression'[7].

This case report carries the limitations of a lack of true sham control (mitigated by lack of response to 2 previous courses), no dedicated scales for anxiety or anhedonia symptoms, and the need for replication. However, in light of successful previous results in OCD, a randomized sham-controlled pilot study of 1 Hz right OFC-rTMS in MDD may be warranted. If successful, OFC-rTMS may provide a new treatment option in MDD where both medications and conventional rTMS fail.

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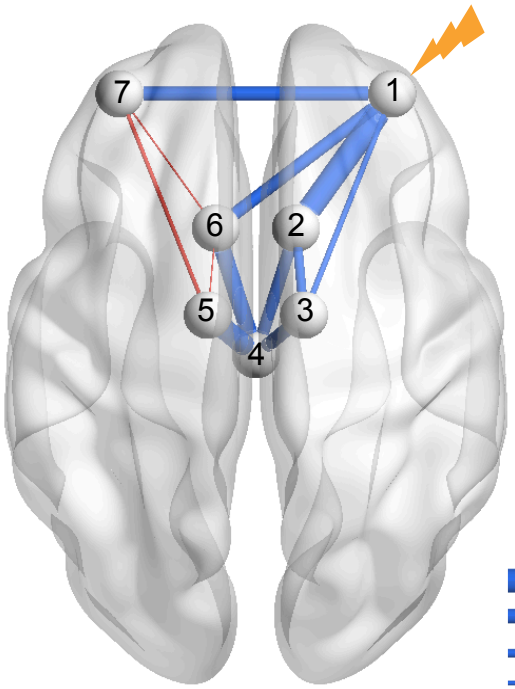
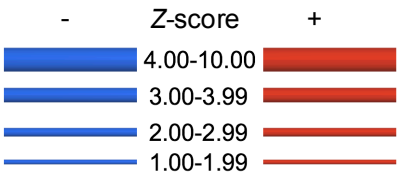
Figure Caption:

Functional connectivity changes between the nodes of the reward circuity following 1 Hz right OFC-rTMS. A red line indicates an increase in functional connectivity between two nodes, while a blue line indicates a decrease in functional connectivity between two nodes. The thickness of the lines indicates the statistical significance of connectivity change (*z*-score). The stimulation site is indicated with the yellow electrical symbol. Numerical Z-scores for the changes in functional connectivity between each pair of regions are tabulated on the right. * indicates a significant change in functional connectivity at $p < 0.05$; ** indicates a significant change in functional connectivity at $p < 0.01$; *** indicates a significant change in functional connectivity at $p < 0.001$. *rLOFC = right lateral orbital frontal cortex*; rNAcc = *right nucleus accumbens*; rMDT = *right medial dorsal thalamus*; VTA = *ventral tegmental area*; lMDT = *left medial dorsal thalamus*; lNAcc = *left nucleus accumbens*; lLOFC = *left lateral orbital frontal cortex.* The changes in connectivity were visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).



Nodes:
1 – rLOFC
2 – rNAcc
3 – rMDT
4 – VTA
5 – lMDT
6 – lNAcc
7 – lLOFC



Region	rLOFC (1)	rNAcc (2)	rMDT (3)	VTA (4)	lLOFC (5)	lNAcc (6)
rLOFC (1)						
rNAcc (2)	-6.00***					
rMDT (3)	-1.67*	-2.54**				
VTA (4)	-0.19	-3.27***	-3.65***			
lLOFC (5)	-3.75***	-2.35**	0.97	1.04		
lNAcc (6)	-3.39***	0.26	0.13	-4.32***	0.69	
lMDT (7)	-0.21	-1.68*	-0.62	-5.41***	1.24	0.59