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Accelerated Neuromodulation Therapy for Obsessive-Compulsive Disorder

Nolan R. Williams[1,*], **Keith D. Sudheimer**[2,*], **Eleanor J. Cole**[1,*], **Andrea D. Varias**[1], **Andrea N. Goldstein-Piekarski**[1,3], **Patrick Stetz**[1], **Anthony Lombardi**[1], **Maria Filippou-Frye**[1], **Peter van Roessel**[1,4], **Kelley Anderson**[1], **Elizabeth A. McCarthy**[1], **Brianna Wright**[1], **Thasveen Sandhu**[1], **Sindu Menon**[1,3], **Booil Jo**[1], **Lorrin Koran**[1,#], **Leanne M. Williams**[1,3,4,#], **Carolyn I. Rodriguez**[1,3,#]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA

[2]Department of Anatomy, Southern Illinois University School of Medicine, Carbondale, IL

[3]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

[4]Mental Illness Research, Education, and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA

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Letter to the Editor

An accelerated course of modified continuous theta-burst stimulation (cTBSmod) shows potential as a treatment for neurological conditions like spatial neglect symptoms in patients with right-hemispheric stroke;[1] however, its potential in other neuropsychiatric disorders remains unknown. Patients with obsessive-compulsive disorder (OCD) are in particular need of novel therapeutic interventions, since they usually experience considerable residual symptoms despite treatment. OCD symptoms are associated with cortico-striatal circuit hyperactivation, right orbitofrontal cortex hyperactivation, and increased functional connectivity between the orbitofrontal cortex and the striatum.[2, 3] This cortico-striatal hyperactivity normalizes following successful treatment.[4]

To test whether an accelerated course of cTBSmod could induce rapid clinical responses in other populations, we conducted an open-label trial of accelerated cTBSmod protocol targeting this frontal-striatal circuit and assessed symptom reduction in seven OCD patients. Using modified cTBS parameters, we delivered multiple cTBSmod sessions daily. We added

Correspondence to: Dr. Nolan Williams (nolanw@stanford.edu) and Dr. Carolyn I. Rodriguez (carolynrodriguez@stanford.edu), Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305.

*,#These authors contributed equally to this work.

Co-Authorship Note: Drs. N. Williams, Sudheimer, and Cole are co–first authors and contributed equally to this work. Drs. Koran, L.M. Williams, and Rodriguez are co–last authors and contributed equally to this work.

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individualized functional connectivity magnetic resonance imaging (fcMRI)-guided targeting to optimally target the frontal-striatal circuit and delivered high-dose stimulation, based on evidence suggesting standard once-daily, 6-week TMS protocols may be under-dosing.[5] We used a variant of the spaced delivery, high-dose, individualized fcMRI-guided targeting method previously applied in treatment-resistant depression.[5] Since altered activation in front-striatal circuits—probed by tasks that require resolution of conflict [6, 7] and inhibitory control [8]—suggests brain regions implicated in cognitive control may be linked to OCD, we explored brain activation before and after treatment probed by a task that requires inhibitory cognitive control (Go/No-Go).[9]

Between 7/2018 and 7/2019, eligible participants were recruited from the community by advertisements and referrals. Eligibility included being age 18 to 80, meeting OCD DSM-5 criteria, with at least moderate symptoms (Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] score ≥ 18), and having failed ≥ one prior adequate trial (using APA Guidelines' dose and duration definitions) of first-line OCD treatment (SRI or CBT). The Stanford Institutional Review Board approved the study, and all participants provided written informed consent. Participants who were already taking an SRI remained on a stable dose for ≥ 12 weeks before study entry. Exclusion criteria were: severe depression (Hamilton Depression Rating Scale [HDRS-17] > 20); age of OCD onset > 30 years; comorbid medical or psychiatric conditions making participation unsafe; or taking medications that increase cortical excitability, inhibit brain excitability, or create hazard with TMS. Subjects planning to commence CBT within 8 weeks before enrollment were also excluded. Independent raters administered the Y-BOCS (primary outcome measure) weekly for 4 weeks. Response was defined *a priori* as a ≥ 35% reduction in Y-BOCS score. The primary outcome was change in Y-BOCS score at Day 14.

Before beginning the accelerated cTBSmod protocol, each participant completed a neuroimaging session that included a resting sequence for determining a personalized frontal pole TMS target and task-based fMRI elicited by the Go/No-Go task (Supplementary Material). All scans were acquired using a 3-tesla GE Discovery MR750 scanner with a NOVA Medical 32-channel head coil and a 3x accelerated multi-band (simultaneous multi-slice) imaging sequence with a repetition time of 2 seconds.

The resting state fMRI sequence was acquired to generate each participant's personalized right frontal pole TMS target (Supplementary Material). The right frontal pole subunit showing greatest connectivity across all the ventral striatum subunits was selected as the stimulation target in each participant (target generation methods and commentaries are provided elsewhere).[5, 10]

Participants received 5 consecutive days of accelerated cTBSmod to the right frontal pole. Each cTBSmod session was comprised of 1800 pulses, delivered in a continuous train of 600 bursts. Each burst contained 3 pulses at 30 Hz, repeated at 6Hz.[1] Ten sessions were applied per day (18,000 pulses/day, hourly) (90,000 total pulses) using a Magventure Magpro X100. Stimulation was delivered at 90% resting motor threshold (depth corrected). Localite Neuronavigation System was used to position the TMS coil over the individualized stimulation target.

Mann-Whitney nonparametric test with Y-BOCS change score as outcome was conducted to determine the group difference (responders vs nonresponders) in magnitude of change in left and right DLPFC activity, elicited during inhibitory control, from before to after treatment with the cTBSmod protocol. The Wilcoxon signed rank test (i.e., paired test) was used to determine within individual differences between left and right side of the DLPFC in cognitive control activation evoked by the No-Go condition of the Go/No-Go task. One participant was removed from the neuroimaging analysis due to excess motion.

Table 1 displays patients' clinical characteristics and OCD symptom severity over time. OCD severity was moderate at baseline (mean Y-BOCS score 27.4, SD=4.7), and mean illness duration 32 years (SD=14.1). Subjects were treatment-resistant; the mean number of prior adequate SSRI trials was 4 (SD=2.2), and 86% (6/7) had failed an adequate trial of cognitive behavior therapy (CBT) with exposure and response prevention. No serious adverse events occurred, side effects were minimal, including transient headache (n=4) and fatigue (n=3) during stimulation. Following cTBSmod, the response rate at the primary outcome time point (Day 14) was 57%, and the overall response rate at ≥ 1 time point was 71%. Y-BOCS score reduction from baseline to Day 14 was statistically significant (Wilcoxon signed rank test $Z=-2.371$, $p=.018$), as was Y-BOCS score reduction from baseline to lowest time point (range 7–28 days) (Wilcoxon signed rank test $Z=-2.366$, $p=.018$). At Day 14, three participants no longer met diagnostic criteria for OCD.

Y-BOCS change score responders showed greater decrease in DLPFC activation than nonresponders, bilaterally, during inhibitory cognitive control activation evoked by the No-Go condition of the Go/No-Go task, following cTBSmod ($p=0.05$; Mann Whitney nonparametric test; Supplementary Material).

This pilot study provides preliminary evidence of the safety, feasibility, and efficacy of a 5-day individualized, accelerated, high-dose, cTBSmod protocol for treatment-refractory OCD that produced a response rate at ≥ 1 time point of 71%. Only minimal side effects were experienced. These results complement Cazzoli, Muri, Schumacher, et al. [1]'s finding that daily cTBSmod sessions can rapidly induce clinical response. Two participants were nonresponders, perhaps reflecting their need for higher pulse dose or a different stimulation site, such as left frontal pole. Accelerated, high-dose, cTBSmod protocol targeting the right frontal pole may offer a new rapid, noninvasive OCD treatment modality. Controlled trials are needed to test these promising findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declarations of Competing Interest:

Dr. N. Williams is a named inventor on Stanford-owned intellectual property relating to accelerated TMS pulse pattern sequences and neuroimaging-based TMS targeting. He is also on the Scientific Advisory Board for NeuraWell, Otsuka, and Halo Neuroscience.

Dr. K.D. Sudheimer is a named inventor on Stanford-owned intellectual property relating to accelerated TMS pulse pattern sequences and neuroimaging-based TMS targeting. He also holds current equity positions in Crispr Therapeutics as well as Moderna, Inc.

Dr. L.M. Williams has served as a consultant for BlackThorn Therapeutics in the last three years, and she currently receives advisory board fees from the Laureate Institute for Brain Research and PsyberGuide of One Mind Institute. She holds patents unrelated to the current study's protocols: US Patents 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data.

In the last three years, Dr. C. Rodriguez has served as a consultant for Epiodyne, received research grant support from Biohaven Pharmaceuticals, and a stipend from APA Publishing for her role as Deputy Editor at The American Journal of Psychiatry.

All other authors report no additional financial or other relationships relevant to the subject of this manuscript.

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Table 1

Participant (n=7) clinical characteristics and OCD symptom severity change over time

Participant	Age/Sex	Illness duration (years)	Trials of SSRI	Trials of CBT	YBOCS Day 0	YBOCS Day 7	% Change from Day 0	YBOCS Day 14	% Change from Day 0	YBOCS Day 21	% Change from Day 0	YBOCS Day 28	% Change from Day 0
1	28/F	23	2	0	28	7	−75%	6	−79%	6	−79%	5	−82%
2	39/M	29	2	1	30	27	−10%	15	−50%	22	−27%	26	−13%
3	70/M	61	6	2	26	27	4%	23	−12%	31	19%	26	0%
4	48/M	43	4	1	19	7	−63%	6	−68%	6	−68%	8	−58%
5	31/M	24	7	1	26	12	−54%	21	−19%	22	−15%	21	−19%
6	31/F	28	6	1	36	30	−17%	33	−8%	35	−3%	33	−8%
7	31/M	16	1	1	24	12	−50%	6	−75%	3	−88%	3	−88%