HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Am J Psychiatry. 2021 May 01; 178(5): 459–468. doi:10.1176/appi.ajp.2020.20060821.

Experimental Manipulation of the Orbitofrontal Cortex Impacts Short-Term Markers of Human Compulsive Behavior: A Theta Burst Stimulation Study

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Abstract

Background: Compulsive behaviors (CBs) are core features of obsessive-compulsive spectrum disorders but appear across a broad spectrum of psychological conditions. It is thought that compulsions reflect a failure to override habitual behaviors “stamped in” through repeated practice and short-term distress reduction. Animal models suggest a possible causal role of the orbitofrontal cortex (OFC) in CBs, but human studies have largely been limited by correlational designs (e.g., cross-sectional comparisons).

Methods: Following a baseline assessment, 69 individuals with CB disorders were randomized in a double-blind, between-subjects design to receive a single session of one of two active stimulation conditions targeting the left OFC—intermittent Theta Burst Stimulation (iTBS), expected to increase OFC activity, or continuous TBS (cTBS), expected to decrease activity (both conditions:600 pulses at 110% target RMT). In both conditions, brain modulation was paired with a subsequent computer task providing practice in overriding a clinically relevant habit (an overlearned shock avoidance behavior), delivered during the expected window of OFC increase/decrease. Pre-post assessments of target engagement (fMRI) and CBs performed in response to an idiographically designed stressful laboratory probe were acquired.

Results: cTBS and iTBS modulated OFC activation in expected directions. cTBS, relative to iTBS, exhibited a beneficial impact on acute laboratory assessments of CBs at +90min post-TBS. Following cTBS, these acute behavioral effects persisted at +1-week.

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Financial Disclosures. All authors reported no biomedical financial interests or potential conflicts of interest.

Conclusions: Experimental modulation of OFC, within the behavioral context of habit override training, impacted short-term markers of CB vulnerability. Findings help delineate a causal translational model, serving as an initial precursor to mechanistic intervention development. [clinicaltrials.gov: NCT03265015, "Theta Burst Stimulation for Compulsive Behavior Non-invasive Brain Stimulation Study"]

Keywords

theta burst stimulation; transcranial magnetic stimulation; compulsive behaviors; obsessive-compulsive disorder; orbitofrontal cortex; habit; goal-directed behavior

Introduction

Compulsive behaviors (CBs) are prominent across a wide range of psychiatric disorders, notably in CB Spectrum Disorders (e.g., Obsessive-Compulsive Disorder), and are associated with marked impairment and staggering societal burden(1). In all their diverse manifestations, CBs can be characterized as a failure of flexible goal-directed behavior to override habitual behaviors(2). While these behaviors may serve a function initially (e.g., short-term reduction of distress, perception of greater certainty), they typically become highly aversive and are recognized as contrary to life goals.

'Dual-system' theories of instrumental action(3) posit that the decision to perform an action is determined by the balance between the habitual system, supporting inflexible stimulus-response associations that are "stamped in" through repetition, and the goal-directed system, which supports flexible application of knowledge and motivational contingencies. Neuropsychological executive deficits in OCD patients (e.g., deficits in set-shifting, reversal learning, and response inhibition) are potentially consistent with a core imbalance in the ability to flexibly implement goal-directed behavior and override habit(4,5). Recent studies have more specifically suggested that, in the context of habit formation, goal-directed behavior is impaired in patients with CBs(e.g.,6,7).

Both animal and human findings converge on alterations within cortico-striato-thalamo-cortical (CSTC) circuits as a key factor in CBs, and highlight one key structure in particular —the orbitofrontal cortex (OFC). However, ambiguity persists regarding the OFC's role as either a driver or an overrider of CBs. The dominant neurocognitive account of imaging findings in OCD suggests that greater activation of a 'direct,' excitatory, feed-forward CSTC pathway relative to an 'indirect,' inhibitory pathway results in overall hyperactivation of CSTC circuits(8,9). This includes hyperactivity in the OFC at rest and during symptom provocation, one of the best-replicated neuroimaging patterns in OCD patients(10). However, *decreased* activation of the OFC is observed in OCD during some cognitive tasks(10), consistent with the OFC's critical role in promoting goal-directed behavior. Furthermore, a large meta-analytic effort recently failed to identify consistent cortical thickness abnormalities in the OFC(11). Such inconsistencies likely reflect the inherent imprecision of correlational methodologies, fMRI susceptibility artifacts within OFC, heterogeneity among patients, and the OFC's diverse and non-static role within CSTC loops,

supporting a broad array of behavioral responses via pathways within and beyond CSTC circuits.

The correlational nature of both neural and neuropsychological findings in patients hinders differentiating neural patterns that are causal in producing CBs from those that are effects or ‘epiphenomena.’ In contrast, animal research techniques afford exquisite experimental precision in modulating neural circuitry relevant to CB and measuring downstream behavioral effects. Such studies have demonstrated a causal role for the OFC in modulating CBs and habit, yet the direction of effect remains ambiguous. Optogenetic studies in rodents(12) have established that brief but repeated activation of mOFC->ventral striatum glutamatergic synapses induces excessive grooming behavior in mice(10,13). Optogenetic disruption of activity in a nearby vmPFC region blocked habit formation and expression in rats(14,15), further suggesting the OFC helps drive habit and CBs. However, the OFC plays an equally critical role in promoting goal-directed behavior. Consequently, chemogenetic inhibition of OFC can disrupt goal-directed behavior in mice, while optogenetic OFC activation increases goal-directed behavior(16) and inhibitory control over a habitual grooming response(17).

The direct relevance of these opposing mechanisms to humans who engage in problematic CBs, and the ability to harness these insights in the development of novel treatments, remains unclear without a direct parallel test of causality in humans to explicate the OFC’s directional role. This is particularly critical given that cross-species comparisons suggest important discrepancies between findings with regard to the OFC’s functions and functional organization that make rodent homologues an imperfect approximation of humans(18). Theta Burst Stimulation(19) (TBS; a form of Transcranial Magnetic Stimulation, TMS) has been used for non-invasive causal manipulations to acutely, experimentally manipulate brain function in two opposing directions. TBS may create a 50–60min window of increased (with intermittent ‘bursts’ of stimulation; iTBS) or decreased (with continuous pulses; cTBS) neural activity using a potent, very brief (40–120sec total) approach. Though the majority of TBS studies target motor cortex, data supporting the safety, tolerability, and target engagement of iTBS and cTBS targeting OFC/frontopolar cortex (FPC) has recently begun to accumulate in healthy volunteers(20) and clinical populations(21).

However, relative to animal models, limitations exist in the spatial and circuit-level precision of currently available methods for non-invasive stimulation in humans, which complicates hypothesis tests given substantial functional heterogeneity within the OFC and neighboring FPC regions(22,23). To overcome this, we used immediate post-TBS completion of a “habit override” task— thereby isolating the specific OFC functional mechanism that we aimed to augment, effectively aiming to “exercise” clinically relevant habit override abilities directly following stimulation.

Here, we used a single session of iTBS and cTBS to test competing hypotheses relevant to the development of a comprehensive pathophysiological model of CBs in human patients: namely, that increased or decreased OFC activation might be beneficial, enhancing patients’ capacity to override CBs. Given spatial diffusion of the TMS signal, with the goal of modulating the OFC at large, we selected a left OFC/FPC target (left Brodmann’s area 10, at

its orbital junction with BA 11) so as to 1) mimic the methods of previous TBS studies that provided crucial validation for the safety, tolerability, and effectiveness (i.e., target engagement) of modulating orbital areas using a standard TMS coil (24,25), and 2) for consistency with a prior TMS study in OCD that also targeted left OFC/FPC and showed clinical benefit(26). To focus the effects of the stimulation, and thereby enhance both the theoretical and clinical implications of findings, TBS was followed immediately by behavioral practice in a habit override task. This provided a behavioral context for the OFC/FPC manipulation and allowed us to ask the more specific question of what role the OFC plays in promoting—or interfering with—the acquisition of a highly clinically relevant skill (overriding avoidance habits). Primary outcomes were: 1) CBF in OFC (target engagement) and 2) participants' acute capacity to override CBs during an idiographic stressful laboratory probe, measured on the same day (TBS +90min) and (in exploratory analyses) at a 1-week follow-up. The study's goal was to establish the first experimental evidence in humans for a mechanistic model in order to inform further experimental work and, ideally, the eventual development of novel mechanistic treatments involving synergistic biological-behavioral pairings(27).

Methods

Design.

The study design (Figure 1) included parallel-arm randomization and patient/assessor blinding. As our primary comparisons were for iTBS vs. cTBS, all participants were allocated to 1 of these 2 arms, using a between-groups design to eliminate crossover and practice effects. However, we used a baseline, single-blind sham TBS lead-in to create parallel procedures at the baseline assessment. As detailed further below and in Figure 1, each of the two principal visits (sham-controlled baseline and active TBS) included: pre-TBS habit acquisition, TBS (sham or active), habit override training, fMRI assessment of target engagement, a 45-min break to allow acute TBS effects to dissipate, and a post-acute (TBS+90min) laboratory probe of CBs. A 1-week follow-up assessment included the laboratory probe of CBs as well as a repeat clinical interview. Clinical assessors were successfully blinded to treatment allocation (see Supplement).

Participants.

78 adults (age 18–55) were randomized and completed all baseline assessment procedures including the single-blind sham TBS session; of these, 69 returned to attempt active TBS (Figure 2). Two clinical inclusion criteria (full details of inclusion/exclusion criteria in Supplement) were used to identify clinically meaningful forms of CB (i.e., both DSM-5 OC spectrum disorders and "diagnostic orphans" with similar problematic CBs): 1) score >1SD above the published mean of healthy controls on at least one self-report scale of CBs; 2) clinically significant CBs per clinician rating on the Yale-Brown Obsessive Compulsive Scale—Compulsions Subscale (Y-BOCS-II(28)). According to baseline diagnostic interviews, these transdiagnostic inclusion criteria yielded a sample with an average of 2.22 DSM-5 OC spectrum diagnoses (see Table 1 for sample characteristics).

TBS.

After determining RMT through standard procedures(29), the TMS coil (MCF-B65 figure-of-8, MagVenture, Denmark) was positioned stereoaxically over a navigational system-identified left-OFC/FPC anatomical target (see neuronavigation details in Supplement).

We followed clinical TMS conventions and adapted published protocols(25) to increase tolerability and comfort and achieved high compliance with TBS procedures, as observed in other clinical populations(21). This included a stimulation ramp-up block (600 pulses beginning at 0% and ramping gradually over the entire block, such that few pulses were delivered at an efficacious amplitude;see Supplement), followed by the active block (600 pulses), which was delivered at the target amplitude of 110% RMT (as in prior OFC/FPC cTBS studies(24)) or at the maximum amplitude tolerated by the participant during ramp-up. Based on findings from TBS clinical studies targeting PFC (30,31) and E-field simulations (Supplement), a minimum tolerated amplitude of 85% RMT was considered adequate for efficacious stimulation and thus participants who completed the active TBS block at =85% RMT (n=59 at 110%; n=4 at 86–104%) were included in all analyses. For these participants, the TBS pulse amplitude as percentage of the maximum stimulator output was 55.8%±6.6% (mean±SD; range: 38%–68%) for cTBS and 52.6%±5.9% (41%–65%) for iTBS.

In all conditions, pulses were applied in a theta burst pattern (bursts of three stimuli at 50 Hz repeated at 5 Hz frequency) using a MagPro X100 stimulator (MagVenture). iTBS consisted of 20 trains, each lasting 2s with intertrain intervals of 8s, for a total of 192s. cTBS consisted of one continuous train of 40s. Sham TBS (delivered to all participants at the baseline session) utilized the participant's allocated active TBS protocol over the same target, run at 20% of maximum stimulator output to provide a consistent absolute level of scalp stimulation and therefore sensation (32–57% of RMT, below the threshold expected to induce reliable cortical effects). See Fig. S2 for a representative computer simulation of the distribution of the electric field induced by TBS in the cortex.

Habit override training.

During the expected window of TBS modulation (on the active TBS day, and during the same window on the sham TBS day), a habit override training task was administered, modeled after previous OCD research(6)(Fig. S1). In brief, in habit acquisition (delivered prior to TBS), participants were instructed that their goal was to avoid receiving shocks to the left and right foot by pressing appropriate buttons whenever a conditioned cue appeared. Across 480 trials (3sec/trial; 24min total), participants overlearned these avoidance behaviors. In the subsequent habit override task (240 trials, 3sec/trial; 12min total), which was administered immediately (15–30min) following TBS, the same pairs of cues were presented, but 1 of the 2 overlearned habits was 'devalued'. A written and verbal instruction was provided informing participants which one of the 2 electrodes had been disconnected and stating they should attempt to resist the relevant 'devalued' avoidance response (i.e., override that habit), while continuing the remaining 'valued' habit. As detailed in the Supplement, performance patterns conformed to expectations and suggested overriding the shock-avoidance habit was challenging for participants.

fMRI assessments.

Data were acquired on a Siemens 3Tesla Prisma Scanner beginning approximately 25min post-TBS (sham or active TBS), immediately following completion of the habit override task, allowing all fMRI collection to occur within the anticipated window of acute TBS modulation. During a 4min resting state block, collected both at the baseline (post-sham TBS) and post-active TBS visits, 2D pseudo-continuous Arterial Spin Labeling (pCASL) was acquired (TR=4.9s;TE=16ms;25 4mm slices with 1mm interslice gap;3.28×3.28mm voxels;labeling duration=1800ms;post-labeling delay=1800ms;25 pairs of labeled/control acquisitions) and preprocessed as recommended using SPM's ASL Perfusion MRI Signal Processing Toolbox (ASLtbx; details in Supplement). pCASL provides stable, interpretable quantification of absolute brain activation (CBF)(32), with adequate test-retest reliability and convergent validity with PET(33,34). A broad prefrontal/anterior mask was defined by all voxels within the MNI template with y≥22. A voxel-wise search was then performed within this mask for clusters differentially modulated by TBS condition (voxel-wise p=.005, map-wise p<.05).

During an additional 7min resting state block, BOLD data were acquired with a multiband/multi-echo (MB-ME) sequence optimized to capture BOLD signal in ventral/OFC regions (TR=1s;TE=13.2, 38.76, & 64.32ms;multiband factor=5;flip angle=49°;matrix=68#x00D7;68;resolution=3mm isotropic voxels;40 oblique slices;480 volumes), which has been found to substantially reduce susceptibility artifact and increases BOLD signal-to-noise by up to 80% in OFC (35–37). Due to budgetary and scanner time constraints, the MB-ME sequence was acquired only at the second MRI visit, following active iTBS or cTBS. At the first session (following sham TBS), a high-resolution structural scan (MPRAGE) was obtained instead, for input to the TMS neuronavigation system. We observed *post hoc* that this customized sequence was indeed less susceptible to signal drop-out in orbital areas relative to pcASL; thus, this secondary measure of left OFC target engagement was used strictly to confirm whether differential modulation extended to anatomically defined left Brodmann's areas 47 & 11, where pcASL signal drop-out was observed.

Following standard preprocessing in AFNI (details in Supplement), to quantify the intensity of spontaneous brain activity during the resting state(38), AFNI's 3dRSFC tool was applied to quantify fractional amplitude of low-frequency (0.01–0.1Hz) fluctuations (fALFF), a putative index of the absolute level of resting activation following TBS. Mean fALFF within *a priori* target regions (left BA 47 & 11, defined within AFNI's TT_Daemon atlas) was extracted for each individual and compared across the two TBS conditions with an unpaired t-test.

Laboratory triggered CB assessment

A laboratory probe of CB vulnerability was completed at the baseline/sham and active TBS visits (90min following TBS) and, as an exploratory probe of the durability of TBS's impact, repeated at the 1-week follow-up visit. We idiographically designed, collaboratively with the participant, a laboratory task involving a triggering object, image, or scenario that corresponded to CBs typical to the participant. The idiographic trigger was presented to the

participant alone in a controlled laboratory environment, along with the means to engage in typical CBs (e.g., hand sanitizer/sink; mirror for skin picking; necessary media for reassurance seeking/checking). To assess ability to voluntarily override CBs, participants were instructed to confront the trigger and then resist or decrease CBs to the extent possible, and were then left alone for 5min. Post-task ratings of urges (0–100), effort (0–100), and success (i.e., total estimated duration of time spent engaged in CBs) were collected. Ratings were correlated with a gold-standard clinical measure of CB severity (Table S1), suggesting we captured clinically relevant symptomatology, but on an immediate timescale suitable for sensitively capturing an acute clinical impact.

See Supplement for detailed "Analytic Strategy" including rationale for per-protocol analyses.

Results

Can we modulate the OFC/FPC target in humans?

Tolerability.—The two conditions were equally well-tolerated [cTBS: 94% (n=33/35) tolerated stimulation at ≥85% RMT; iTBS: 88% (n=30/34); Fisher's exact p=.43]; further details in Supplement. No serious or unanticipated adverse events occurred.

pcASL.—The pcASL sequence acquired both before (at the baseline/sham TBS visit) and after active cTBS/iTBS showed that TBS condition moderated pre-to-post-TBS changes in CBF in the target area of BA 10 and a surrounding ventromedial (vm)PFC area (voxel-wise $p_{uncorrected}$<.005, n=736 voxels within PFC mask, map-wise $p_{corrected}$<.01;partial η^2=.21;Fig 3B), with the expected direction of modulation observed for both cTBS (decrease: *post hoc* paired t_{30}=−2.17;p=.038;d=0.39) and iTBS (increase: paired t_{26}=3.14;p=.004;d=0.68).

fALFF. Lower fALFF was observed following cTBS, relative to following iTBS, in the left BA 47 (t_{57}=−2.02;$p_{uncorrected}$=.048; Cohen's d=0.53) but not left BA 11 (t_{57}=0.27;$p_{uncorrected}$=.79;d=0.07).

Does OFC/FPC modulation, in the context of habit override training, have an acute effect on CBs?

In linear mixed models focusing on the two primary timepoints (baseline and active TBS +90min), group*time interactions were observed on laboratory measures of CB urge strength (β=20.32;t(60)=3.28;$p_{uncorrected}$=.002;$p_{FDR\text{-}corrected}$=.006;$r_{effect\ size}$=.39) and time spent engaged in idiographic CBs (β=0.45;t(60)=2.45; $p_{uncorrected}$=.017;$p_{FDR\text{-}corrected}$=.026;$r_{effect\ size}$=.30). For effort needed to resist CBs, the interaction was non-significant (β=12.25;t(60)=1.71; $p_{uncorrected}$=.093;$p_{FDR\text{-}corrected}$=.093;$r_{effect\ size}$=.22), although a significant pre-to-post reduction was observed in the cTBS group (p=.032;d=™0.39) but not the iTBS group (p=.85;d=−0.04). Across all three indices (Figure 4), the pattern of change suggested cTBS produced pre-to-post improvements, while indices were unchanged or (non-significantly) worsened following iTBS.

Across individuals, larger CBF reductions in the vmPFC functional ROI (Fig 3C) from pre-to-post active TBS correlated with larger reductions in urge strength (r=.32; $p_{uncorrected}$=.015;$p_{FDR\text{-}corrected}$=.045) and time spent in CBs (r=.32; $p_{uncorrected}$=.015;$P_{FDR\text{-}corrected}$=.023), but not effort (r=-.02;$p_{uncorrected}$=.88;$p_{FDR\text{-}corrected}$=.88).

In exploratory within-group analyses probing the durability of change at the 1-week follow-up, in the cTBS group, significant decreases from baseline to 1-week follow-up were observed in urge strength (paired t_{30}=−3.39;$p_{uncorrected}$=.002;$p_{FDR\text{-}corrected}$=.006;d=0.76), time spent in CBs (paired t_{30}=−2.51;$p_{uncorrected}$=.018;$p_{FDR\text{-}corrected}$=.027;d=0.46), and effort needed to resist (paired t_{30}=−2.28;$p_{uncorrected}$=.030;$p_{FDR\text{-}corrected}$=.03;d=0.51)(Figure 4), while no significant enduring effects were found for iTBS ($p_{uncorrected}$'s>.31;d's=0.07–0.25).

Discussion

In the present study, a single session of intermittent or continuous TBS was successful in 1) increasing and decreasing (respectively) CBF within the left OFC/FPC (BA 10) and surrounding vmPFC areas (Figure 3), and 2) modulating left ventrolateral OFC (BA47), according to a secondary index of spontaneous brain activity (fALFF). Furthermore, the single, 40-second session of cTBS, paired with the context of behavioral training in habit override, reduced acute markers of clinically relevant CBs measured in the laboratory, relative to iTBS (Figure 4). Acute in-laboratory behavioral improvements in the cTBS condition endured at a 1-week follow-up period, with medium-to-large effect sizes. Though this suggested possible durability that exceeded what would typically be expected following a single session of rTMS delivered in isolation (i.e., without a paired behavioral manipulation), effects of the brief, single-session manipulation did not extend to clinical symptom scales that measure more generalized and enduring symptomatic patterns (see Supplement).

Our findings add to a growing body of published studies suggesting brief, non-invasive TBS procedures can impact resting/baseline activation in the OFC/FPC and nearby ventral mPFC areas—even when using a standard figure-of-8 TMS coil(e.g.,24,25). Notably, consistent with expected spatial diffusion of TMS signal, evidence of target engagement extended to a broader mPFC area, suggesting modulation of a wider PFC network with the potential to influence a broad range of functions.

Neuroanatomical models of OCD, which center broadly on CSTC circuits, have provided important groundwork, but progress has been hindered by the inherent limitations of correlational (e.g., cross-sectional group comparison) designs in humans. Here we circumvented that limitation by performing causal TBS studies, which led to findings consistent with animal experiments (e.g. optogenetic stimulation of the OFC produced excessive grooming in mice(10,13)). By decreasing OFC/FPC activity in CB patients via cTBS, we posit that we may have pulled a chronically hyperactive OFC state down from the "ceiling," opening a window of opportunity for more reflexive OFC activation and adaptive, goal-directed learning to occur. Within this window of opportunity, behavioral training

might provide critical opportunities to make clinical effects of neuromodulation more efficient, stronger, and/or more enduring. Similarly, a multi-site RCT of "deep TMS" targeting the medial PFC/anterior cingulate suggested that active stimulation outperformed sham in reducing OCD symptoms, when both active and sham TMS were paired with the context of a pre-stimulation behavioral manipulation (brief exposure to a trigger)(39). This led the FDA to approve marketing of deep rTMS to OCD patients, provided the behavioral exposure context protocol is specifically followed, under the assumption that this behavioral framing may be an influential factor. "State-dependent" neuromodulation(40–42) may thus play a key role within emerging theory-driven, synergistic biological-behavioral treatments(27).

Limitations.

The study was well-powered only to detect medium effect sizes or larger; yet several such effects were detected. Per-protocol analyses, which measure the effect of using (i.e., tolerating) a given treatment, have less real-world clinical relevance and greater possibility of selection bias than intent-to-treat (ITT) analyses, which measure the effect of merely being assigned/randomized to a treatment; future well-powered studies should confirm these initial findings using an ITT principle. Emerging motor physiology work suggests the directionality of TBS effects are impacted by a complex interaction between RMT, cortical depth, and number of pulses(e.g.,43), suggesting future work would be optimized by a more idiographic and nuanced approach to dosimetry(e.g.,44). Furthermore, neural target engagement was quantified as single-point averages reflecting spontaneous/baseline activation in *a priori* regions, whereas TBS effects on network-level activation and functional connectivity may be broad and dynamic(45). Future, definitive experimental studies should include: 1) both sham and cTBS treatment arms, with and without habit override training—to thoroughly assess key unanswered questions about necessary and sufficient intervention components; 2) larger samples permitting diagnosis-specific analyses, particularly in an effort to better delineate effects on relatively "compulsive" vs. relatively "impulsive" behaviors(46–48); and 3) healthy controls, to assess whether procedures "normalize" neural and/or behavioral patterns. Such rigorous experimental studies will serve as essential precursors to facilitate optimized, mechanistically targeted treatment development.

Conclusion.

We posit that by decreasing drive towards habitual and compulsive behaviors, down-regulation of the OFC/FPC (via cTBS) may provide a window of opportunity in which to enhance goal-directed behavior, after first "muting" OFC-mediated habit system interference. Our novel, fully automated behavioral training in habit override may have leveraged this acute brain state, creating a short-term benefit observed specifically on idiographic CBs, which persisted for 1-week. Results advance an integrative picture of both neural and behavioral pathophysiological processes that contribute to CBs. Future studies would benefit from inclusion of crucial experimental controls (e.g., sham TBS, cTBS without habit override) to clarify the role that behavioral context may play in leveraging an acute OFC/FPC state manipulation. With further extension of these initial experimental findings, this line of inquiry could represent a first step towards developing and clinically

optimizing neuromodulation therapies (e.g., multi-session synergistic bio-behavioral treatments) that are well-grounded in basic experimental science and leverage acute neuroplasticity to maximize clinical benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This research was supported by NIH R21MH112770 and by the Clinical and Translational Sciences Institute at the University of Pittsburgh (UL-TR-001857). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We gratefully acknowledge Daniel M. Blumberger, MD, Sabine Wilhelm, PhD, the study participants, and all members of the Clinical Application of Neuroscience lab for their contributions to this work.

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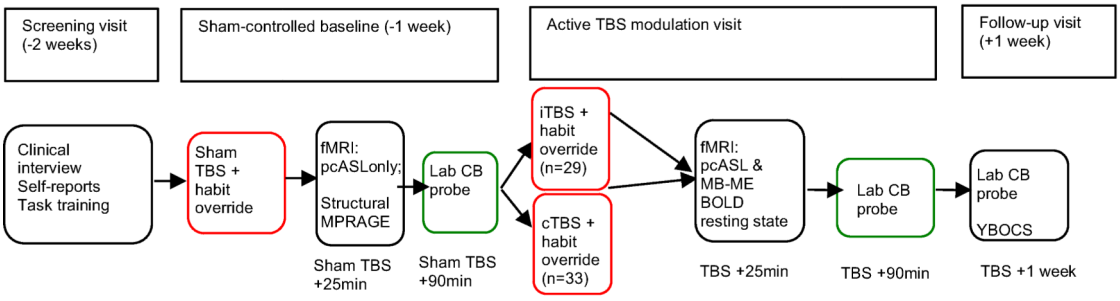


Figure 1. Flowchart illustrating study design.

Based on TBS meta-analyses in motor cortex (49), acute increases (iTBS) and decreases (cTBS) were expected to persist for approximately 50–60min following the active TBS session, with large effect sizes peaking 10–15min post-TBS (i.e., during the habit override training task). Preliminary findings further suggested that effects of similar TBS protocols might extend to dorsolateral and medial PFC/OFC regions (20,24,50–52). All study procedures were approved by the University of Pittsburgh Institutional Review Board.

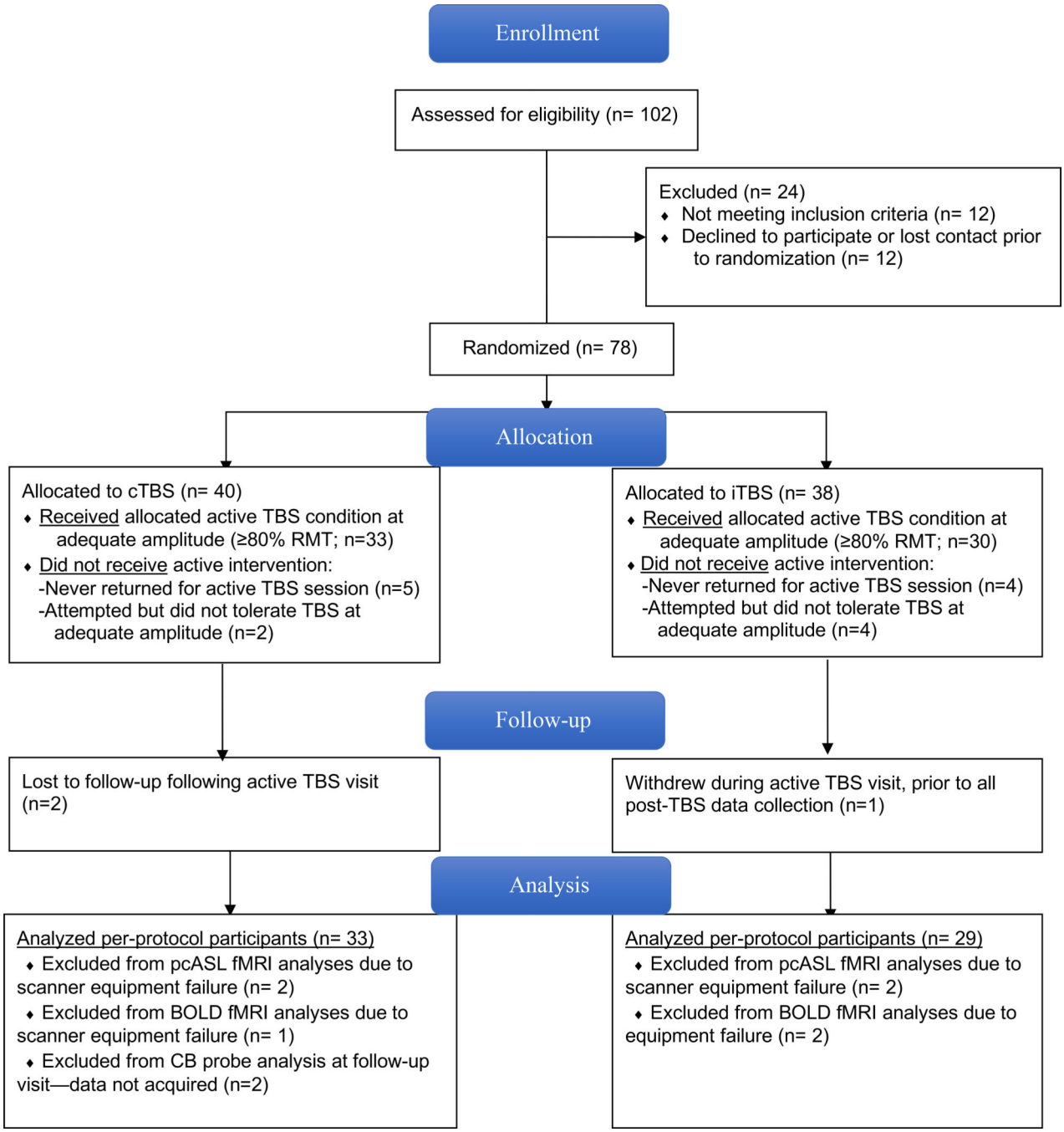


Figure 2.

CONSORT diagram detailing the flow of participants through the study. Of note, according to unpaired t-tests (continuous variables) and Chi-squared tests (categorical variables), the participants excluded from all analyses (n=16) did not differ at baseline from the analyzed sample (n=62) on any neural or behavioral (CB probe) outcome measure (*p*'s>.30), nor on any demographic or clinical features reported in Table 1(*p*'s>.24). No follow-up data was acquired for any participant who dropped out midway through the study, as we were unable to reach these participants for re-assessment.

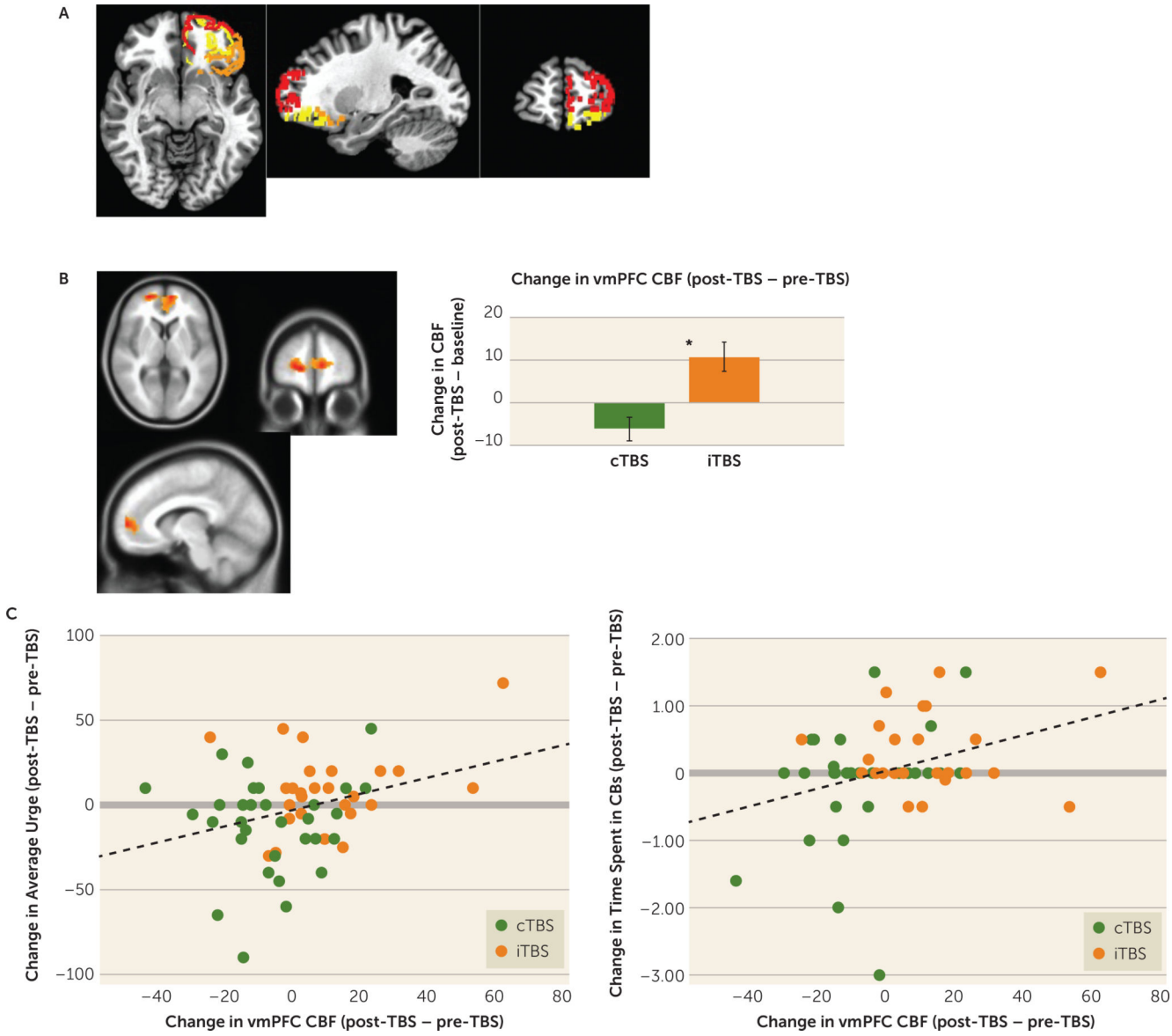
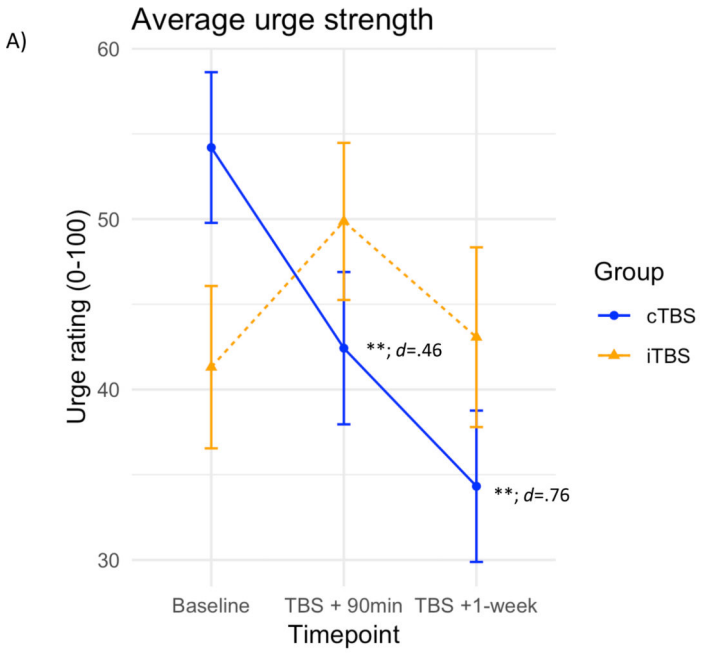
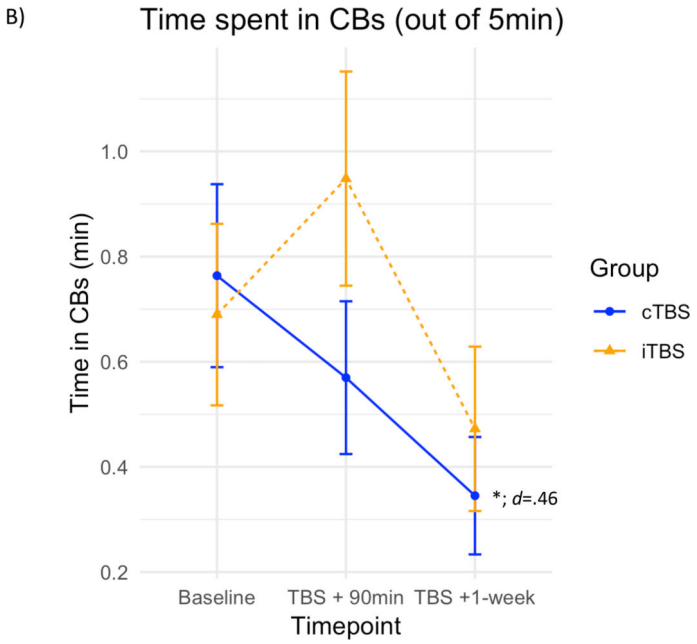


Figure 3.

A) *A priori* anatomical stimulation target area (left orbitofrontal cortex/frontopolar cortex) and anatomical subregions. For participant-level neuronavigation on the active stimulation day, the target location reflecting a focal point of stimulation within left Brodmann's area 10 was verified on the basis of each participants' individual structural MPRAGE acquired at the baseline scan (details in Supplement**)**. Brodmann's area 10 shown in red, Brodmann's area 11 shown in yellow, Brodmann's area 47 shown in orange. B) A voxel-wise search, performed within a broad prefrontal cortex brain mask, identified a cluster in which the pre-to-post-TBS change in cerebral blood flow (CBF), captured at rest with a pseudocontinuous Arterial Spin Labeling (pcASL) sequence, was modulated by TBS condition (voxel-wise $p<.005$, within-mask map-wise corrected $p<.01$, n=736 voxels). The cluster spanned orbitofrontal/frontopolar (Brodmann's area 10) and neighboring ventromedial prefrontal cortex (vmPFC) areas, with local maxima in both left Brodmann's area 10 (x=−8, y=56,

z=4) and right Brodmann's area 10 (x=16, y=56, z=0). Within this cluster, according to *post hoc* paired t-tests comparing the baseline scan to the post-TBS scan, cTBS significantly reduced CBF (t_{30}=−2.17;p=.038;d=0.39) and iTBS significantly increased CBF (t_{26}=3.14;p=.004;d=0.68). Values displayed are mean? SEM. C) Scatterplots depicting correlations between change scores (post-TBS at active TBS visit – baseline visit) in vmPFC CBF (cluster depicted in panel B above) and behavioral outcomes (urge strength, time spent in CBs) across all participants. Across individuals, larger CBF reductions in CBF correlated with larger reductions in urge strength (r=.32; $p_{uncorrected}$=.015;$p_{FDR\text{-}corrected}$=.045) and time spent in CBs (r=.32; $p_{uncorrected}$=.015;$p_{FDR\text{-}corrected}$=.023).





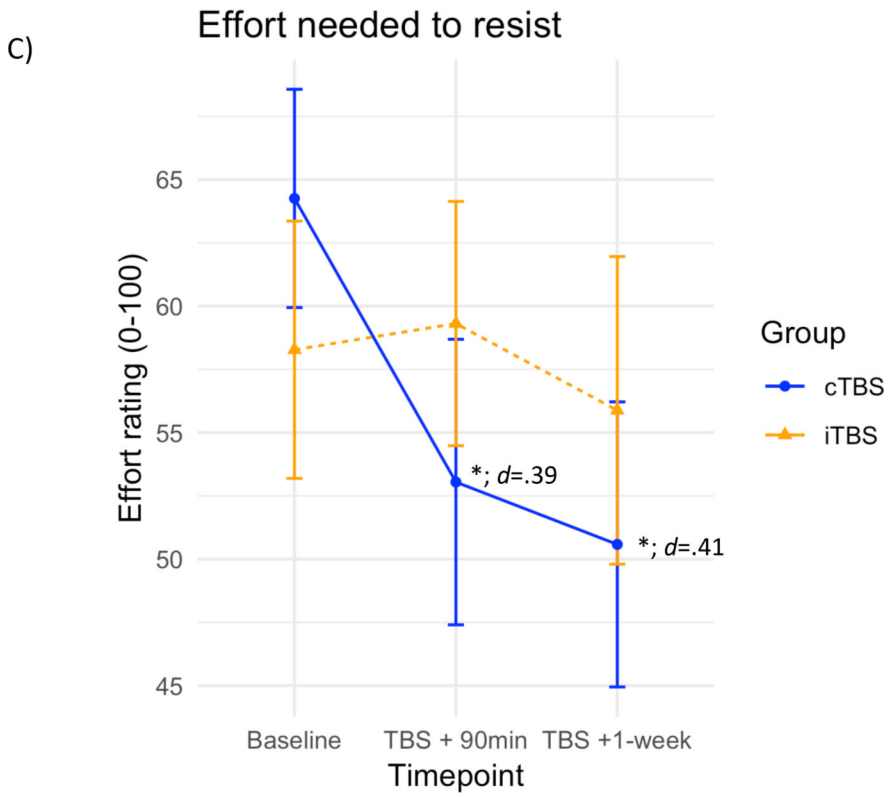


Figure 4.

Among participants randomized to cTBS (n=33), relative to the baseline/sham-TBS visit, active cTBS followed by habit override training led to decreased A) urges to complete compulsive behaviors, B) time spent performing compulsive behaviors, and C) effort needed to resist compulsive behaviors during a 5min laboratory probe, with significant effects persisting at a 1-week follow-up. Participants randomized to iTBS (n=29) exhibited either non-significant (trend-level, *p*'s>.07) increases (A, B) or no changes (C) from baseline at 90-min post-TBS, with no significant effects observed at the 1-week follow-up. Values displayed are mean ± SEM. The variables in A-C did not differ significantly at baseline across the cTBS and iTBS samples (omnibus MANOVA $F_{3,59}$=1.3, *p*=.29; uncorrected *p*'s for group difference on individual variables: *p* = .074-.71). **p<.01, *p<.05 for pairwise comparisons within group, comparing each post-TBS time point to baseline value. Cohen's *d* effect sizes, noted on the figure for all significant within-group changes, are calculated with Cohen's classical formula (i.e., unadjusted for repeated measurement), which provides uniform, conservative quantification of standardized effect sizes independent of the study design.

Table 1.

Demographic and clinical characteristics of the sample included in main analyses (n=62)

	Full analyzed sample (n=62)		**cTBS sample (n=33)**		**iTBS sample (n=29)**	
Caucasian, n (%)	53	(90.3%)	27	(82%)	26	(90%)
Female, n (%)	46	(74.2%)	26	(79%)	20	(69%)
Age, mean (SD)	29.85	(9.18)	29.3	(9.0)	30.4	(9.5)
Taking psychotropic medication, n (%)	25	(40%)	13	(39%)	12	(40%)
Principal diagnoses, n (%)						
Obsessive Compulsive Disorder (OCD)	32	(51.6%)	16	(49%)	16	(55%)
Excoriation Disorder	19	(30.6%)	11	(33%)	8	(28%)
Trichotillomania	7	(11.3%)	3	(9%)	4	(14%)
Body Dysmorphic Disorder	4	(6.5%)	3	(9%)	1	(3%)
OCD diagnosis (principal OR secondary), n (%)	60	(97%)	32	(97%)	28	(97%)
Comorbid depressive disorder, n (%)	23	(37.1%)	11	(33%)	12	(41%)
Generalized anxiety disorder, n (%)	19	(30.6%)	10	(30.3%)	9	(31%)
Eating disorder, n (%)	5	(7.0%)	2	(6%)	3	(10%)
Y-BOCS obsessions subscale	9.13	(4.08)	9.5	(4.1)	8.7	(4.1)
Y-BOCS compulsions subscale **	12.79	(3.07)	13.0	(2.7)	12.6	(3.5)
Y-BOCS total	21.92	(6.08)	30.3	(5.8)	29.7	(6.4)

Note: No variables in the table above differed as a function of group (cTBS vs. iTBS) according to unpaired t-tests (for continuous variables) or Chi-squared tests (for categorical variables) (p's>.43). These variables also did not differ significantly between the randomized (intent-to-treat) sample and the analyzed (per-protocol) sample (p's>.24).

** Although the full Y-BOCS was administered for the purposes of clinical characterization, only the compulsions subscale, which captures transdiagnostic compulsive behavior severity, was utilized as a study inclusion criterion.