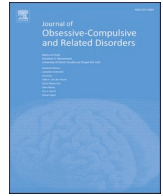




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## Do exposure therapy processes impact the efficacy of deep TMS for obsessive-compulsive disorder?

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## ABSTRACT

This study evaluated exposure therapy processes during symptom provocation in a randomized sham-controlled trial of deep transcranial magnetic stimulation (Deep TMS) for 99 adults with obsessive-compulsive disorder (OCD). The following factors were expected to lead to more symptom improvement, particularly in active relative to sham groups: 1) progression to more hierarchy items, 2) greater distress during provocations, 3) between-session habituation, and 4) variability in distress during provocations. Participants were randomized to six weeks of daily symptom provocation plus sham or active Deep TMS of the dorsal medial prefrontal cortex and anterior cingulate cortex. Obsessive-compulsive symptoms were assessed weekly and at four-week follow-up. No significant predictors were identified though increased distress moderated outcomes ( $b = -.041, p = .048$ ); those who reported more distress during provocations had an improved active vs. sham response, though there was less of a difference between active and sham for those who reported less distress. Lack of an association between other exposure processes and treatment outcome may suggest differences between Deep TMS provocations and exposure exercises.

## 1. Introduction

Noninvasive neuromodulation is a promising therapeutic option for individuals with obsessive-compulsive disorder (OCD). Although evidence-based treatments for individuals with OCD exist, a significant proportion continue to struggle with symptoms even after participating in these treatments (McGuire et al., 2015; Öst et al., 2015). In particular, a specific form of cognitive-behavioral therapy, exposure and response/ritual prevention (ERP), is the first-line treatment for individuals with OCD and has been shown repeatedly to be superior to pill and psychological placebo (McGuire et al., 2015; Öst et al., 2015).

During ERP, patients are challenged to face obsession-provoking situations without engaging in compensatory behaviors (compulsions) and learn that obsessive fears will not occur, or that the distress associated with symptoms is manageable and passes with time, in turn leading to symptom reduction (Foa & McLean, 2016). The leading mechanistic models of exposure therapy, the inhibitory learning (Craske et al., 2008) and emotional processing (Foa & Kozak, 1986; Foa &

McLean, 2016) models, are both based on an extinction learning framework, which assert that during exposure, repeated presentations of a feared situation without a negative consequence leads to safety learning about the obsessive fear (Craske et al., 2008; Foa & McLean, 2016). Several strategies have been proposed to enhance inhibitory learning about feared expectancies, including increasing the diversity of contexts in which exposures are conducted, which may be both external (e.g., exposure stimuli) and internal (e.g., amount of distress experienced), as well as maximizing feared expectancies prior to exposure (Craske et al., 2008). During ERP for OCD, context variability involves varying stimuli with which exposures are conducted (e.g., conducting exposures across symptom dimensions, or across different stimuli within symptom dimensions) (Knowles & Olatunji, 2019), as well as varying the amount of distress evoked by exposure (Kircanski & Peris, 2015); and indeed, more context variability has been associated with improved treatment outcomes during exposure in clinical and analogue samples of individuals with OCD (Kircanski et al., 2012; Kircanski & Peris, 2015). The importance of violating feared expectancies during ERP for OCD

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have been supported by empirical (Guzick et al., 2020) and theoretical work (Jacoby & Abramowitz, 2016). Similarly, research has supported certain processes as indicative of emotional processing during exposure, most consistently “fear activation,” or experiencing fear/anxiety during exposure, as well as “between-session habituation,” or decreased distress upon successive exposure sessions (Foa & McLean, 2016). Foundational research on the emotional processing approach found that both more fear activation and between-session habituation led to improved treatment outcomes in individuals with OCD (Foa et al., 1983; Kozak et al., 1988), though it is worth noting these findings have not been universally replicated (Craske et al., 2008).

Despite the strong efficacy of ERP and a relatively well-developed understanding of its mechanisms, between 20 and 38% of individuals are estimated to not respond to this therapy (Foa et al., 2005; Öst et al., 2015). Non-invasive neuromodulation has been proposed as an alternative treatment for individuals with OCD, and there are now a small number of randomized controlled trials supporting symptom provocation plus non-invasive neurostimulation for this population (Nuñez et al., 2019; Trevizol et al., 2016). In particular, a recent trial showed that brief symptom provocation immediately before high-frequency deep transcranial magnetic stimulation (Deep TMS) of the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) was significantly more effective than symptoms provocation plus sham stimulation (Carmi et al., 2019). Symptom provocations are proposed to activate brain circuitry involved in OCD pathology, specifically abnormalities in cortico-striatal-thalamic-cortical (CSTC) circuits (McGovern & Sheth, 2017; Pauls et al., 2014). Dysfunction in the orbitofrontal cortex and hyperactivity in the dorsal anterior cingulate cortex (dACC) is thought to lead to an imbalance between direct excitatory pathways and indirect inhibitory pathways in individuals with OCD, leading to the repetitive obsessions and compulsions that characterize the disorder (McGovern & Sheth, 2017; Pauls et al., 2014). High-frequency stimulation of the mPFC and dACC has been shown to be more effective than low-frequency stimulation (Carmi et al., 2018). High-frequency stimulation appears to produce a mixed inhibitory-excitatory effect on target regions (Houdayer et al., 2008; Lefaucheur et al., 2014), so while precise mechanisms are not clear, it does appear that these stimulation parameters improves CTSC circuit dysfunction, for example, through improving inhibitory control and error monitoring, thus improving an individual’s ability to dismiss obsessions and resist compulsions (Carmi et al., 2018).

Notably, it may also be the case that stimulation of the mPFC also leads to enhanced extinction learning, as the mPFC is central to the fear extinction circuit (Phelps et al., 2004). A recent study showed that transcranial direct current stimulation of the mPFC prior to an ERP session led to quicker habituation, a marker of safety learning (Adams et al., 2021). Thus, it may be that another mechanism of neuromodulation is through enhanced extinction learning following exposure. That said, extinction learning appears to be mediated by more ventral regions of the mPFC (Phelps et al., 2004) relative to the more dorsal regions stimulated in Deep TMS for OCD (Carmi et al., 2019). Indeed, high frequency stimulation of the ventral mPFC has been more often the target of stimulation to enhance exposure therapy in other anxiety and related disorders (Herrmann et al., 2017; Marin et al., 2014). In fact, hyperactivity of the more dorsal targets of stimulation used in this study (the dACC) have been associated with fear expression, and thus high-frequency stimulation may be expected to inhibit fear learning (Marin et al., 2014). That said, as noted, high frequency and low frequency stimulation have both been shown to have mixed excitatory and inhibitory effects (Houdayer et al., 2008; Lefaucheur et al., 2014), as reflected in the benefits of high-frequency stimulation to hyperactive regions of the CTSC circuit (i.e., mPFC and dACC) for individuals with OCD. Taken together, it is unclear whether Deep TMS of the mPFC and dACC for OCD would enhance or inhibit extinction learning.

Provocation exercises done as part of Deep TMS appear to share similarities to exposure, in that they are explicitly done to evoke

obsessional distress while patients are instructed to resist compulsions. That said, there are also significant differences, most prominently including the duration of exposure exercises (up to 60–90 min in ERP; 3–5 min in dTMS) as well as the degree of therapeutic support during exposure (e.g., personalization and adaptation midway through exposure, coaching in resisting compulsions). Thus, it is also unclear whether leveraging principles of exposure therapy during symptom provocation leads to improved outcomes, and whether those outcomes are amplified when used in conjunction with active vs. sham stimulation. The aim of this study was to test whether extinction learning processes that have been tied to improved outcomes in exposure therapy are related to symptom reduction during brief symptom provocation plus Deep TMS or sham stimulation for individuals with OCD. The sham-controlled nature of this study enables an investigation of both whether exposure processes are evoked during provocation alone (in the sham condition), and whether Deep TMS amplifies these processes through neuromodulation following provocation. This would enable a better understanding of the nature of provocations as well as mechanisms underlying provocation plus active Deep TMS (vs. sham). A better understanding of these mechanisms may provide avenues to optimize treatment.

Based on the leading theoretical models of exposure therapy mechanisms, the inhibitory learning (Craske et al., 2008) and emotional processing models (Foa & McLean, 2016), we hypothesized that four provocation features would be related to improved symptom reduction, and that these effects would be more pronounced in active relative to sham stimulation conditions. First, it was expected that progression to more distressing hierarchy items that involved a wider range of both *in vivo* and imaginal exposures would lead to improved treatment outcomes based on work highlighting the importance of context variability during exposure (Craske et al., 2008; Kircanski et al., 2012; Knowles & Olatunji, 2019). Second, it was expected that greater distress during exposure would correspond with improved treatment outcomes, as higher distress was expected to provoke greater feared expectancies (and thus expectancy violations), as described in the inhibitory learning approach (Craske et al., 2008; Guzick et al., 2020) as well as activation of fear networks that could be further modified via corrective learning, as described in the emotional processing approach (Foa & McLean, 2016). Third, it was experienced that between-session habituation across sessions would correspond with more symptom reduction, consistent with emotional processing theory (Foa et al., 1983; Foa & McLean, 2016; Kozak et al., 1988). Finally, it was expected that more variability in distress during exposure would correspond with improved outcomes due to the proposed importance of context variability in safety learning (Craske et al., 2008) and prior work that has shown a relationship between distress variability and treatment outcome during exposure and response prevention therapy (Kircanski & Peris, 2015). We also expected that these effects would be enhanced in the active relative to sham stimulation condition. Because improved overall outcomes were found in the original trial in active relative to sham stimulation (Carmi et al., 2019), we expected that exposure process variables would be especially potent in the active stimulation group.

## 2. Materials and methods

### 2.1. Participants

One-hundred patients with a primary diagnosis of OCD (as determined by a clinician using the Structured Clinical Interview for DSM-IV) were enrolled in the study across 11 sites; one withdrew during the initial resting motor threshold (RMT) assessment and five were not included as they either had medication changes during the trial ( $n = 4$ ) or had an exclusionary diagnosis ( $n = 1$ ). This resulted in a final analyzed sample of 94, replicating the approach using in the original trial (Carmi et al., 2019). Primary eligibility criteria included: aged between 22 and 68 years old and score  $\geq 20$  on the Yale-Brown Obsessive Compulsive Scale (YBOCS). Additionally, as this study was designed for

patients who had limited response to traditional therapies, there were specific requirements for treatment history; patients were required to either be at maintenance dose levels of serotonin reuptake inhibitors (SRIs) for at least 2 months prior to study involvement or in maintenance cognitive-behavioral therapy, with at least one failed response to an SRI. Participants were permitted to take SRIs, antidepressants, and D<sub>2</sub> or D<sub>2</sub>/5-HT<sub>2</sub> antagonist medications throughout the study provided that there were no medication changes 2 months before becoming involved in the study or during the study. Eligible participants were then randomly assigned to either active Deep TMS treatment or a sham Deep TMS control (both together with symptom provocations). Daily treatments ( $N = 29$ ) were given for the first five weeks and four treatments were given during the final, sixth week (the final day was reserved for a full assessment battery). Further participant information can be found in (Carmi et al., 2019).

## 2.2. Procedures

### 2.2.1. Randomization and blinding

Eligible participants were randomized to sham or active Deep TMS in a 1:1 ratio using a stratified randomization scheme using a random number generator, in which each participant was given a unique randomization code that corresponded with one of the treatment conditions. Participants, Deep TMS operators, and assessors were all blind to treatment condition, as active and sham Deep TMS treatment procedures were designed to be perceived similarly by participants. After treatment, participants were asked whether they believed they received active or sham treatment; 66% of participants in active treatment and 69% of participants in sham were not aware of or incorrectly guessed the type of treatment they received.

### 2.2.2. Provocation description

Prior to every Deep TMS treatment, participants were exposed to a symptom provocation with the goal of engaging neural circuits relevant to their OCD (Carmi et al., 2019). These provocations lasted 3–5 min and were designed by a clinician (psychologist/psychiatrist) and the participant in their first meeting. A variety of provocations were created for each patient and organized from least to most distress provoking, akin to an exposure hierarchy, with the goal during a treatment session to evoke a distress score between 4 and 7 on a scale of 1–10. A certified staff member assisted the participant in evoking this distress and instructed the participant to continually think about the provocation throughout the Deep TMS treatment and reminded the participant during the Deep TMS to continue thinking about the provocation. Both “internal” and “external” provocations were developed, with internal provocations including questions designed to evoke obsessive doubts (e.g., “are you sure you locked your door?”) and external provocations including symptom-relevant stimuli (e.g., a picture of their door unlocked). Participants only moved on to external provocations if internal provocations did not evoke sufficient distress. Provocations for all patients at all sites were reviewed by a central OCD expert in the study. More information about provocation procedure can be found in (Carmi et al., 2019).

### 2.2.3. Deep TMS

A Magstim Rapid2 TMS stimulator with a BrainsWay H7-shaped coil was used. The coil was used to stimulate the dorsal mPFC and the ACC bilaterally (Carmi et al., 2019). To define the optimal placement for stimulation, staff localized the motor cortex and determined the resting motor threshold. Prior to each treatment, the RMT was found by locating where the coil created the most minimal involuntary feet contractions. The Deep TMS H7 coil was placed 4 cm in front of the foot motor cortex at 100% of the leg resting motor threshold (RMT). The treatment group experienced high frequency Deep TMS of the mPFC and (20 Hz) at 100% of RMT, with 2-s pulse trains and 20-s intertrain intervals. Treatment was provided daily for five weeks and four times during the sixth week

(an assessment session was scheduled on the final day).

### 2.2.4. Sham Deep TMS

Participants in the Sham Deep TMS condition underwent the same daily treatment set up and localization procedure, with the stimulator programmed to induce similar scalp sensations without penetration of the electric field into the brain.

## 2.3. Measures

### 2.3.1. Y-BOCS

The 10-item Yale-Brown Obsessive Compulsive Scale (YBOCS) was the primary measure to assess OCD severity and treatment response (Goodman et al., 1989). The measure assesses time occupied by symptoms, interference from symptoms, amount of distress caused by symptoms, resistance against symptoms, and control over symptoms. Y-BOCS scores were gathered at baseline, at the end of weeks 1, 2, 3, and 6 of treatment (end of week 6 being immediate post-treatment), and 10 weeks after beginning treatment (4-week follow-up from the end of acute stimulation treatment). Trained, blinded independent evaluators administered the Y-BOCS at assessment visits and were not present during stimulation sessions.

### 2.3.2. Exposure processes

During each provocation, the following information was recorded: the number of provocations attempted, whether internal or external provocations were used, the hierarchy placement of the provocation, and the subjective distress experienced during the provocation using a 1–10 self-report distress scale. The following variables were extracted for analyses in this study: hierarchy progression/variability in provocation content (measured as the total number of provocations completed along the hierarchy), distress during provocations (measured as mean peak distress during provocations), between-session habituation (measured with a latent slope variable that was calculated by extracting the observed trajectory of distress ratings across trials for each participant), and variability in distress during provocations (measured as the standard deviation of peak distress during provocations).

## 2.4. Analysis plan

This study followed the modified intent-to-treat approach used in the original trial, including a total of 94 participants (100 were enrolled though 6 were not included due to eligibility criteria or dropping out prior to treatment initiation).

First, descriptive data regarding provocations was presented, including the mean and standard deviation of the number of different provocations used, the number of participants completing both external and internal provocations, and the mean and standard deviation SUDS score during provocations.

Next, multilevel models with the Y-BOCS as the dependent variable were conducted, with models nesting visits within participants, enabling an analysis of differences in trajectories as a function of the exposure process variables. Analyses were repeated with 6-week (immediate post-treatment) and 10-week (4-week follow-up) endpoints. Samples sizes of at least 50 with 5 repeated measures have been recommended for multilevel models (Maas & Hox, 2005); this study was considered well-powered under these guidelines with 94 participants and an average of 5.4 Y-BOCS recordings per participant. Predictors were evaluated by testing the effect of time\*an exposure process variable (mean SUDS, number of provocations completed, between-session habituation, SD SUDS), thus testing whether each exposure process corresponded with improved symptom reduction (regardless of treatment condition). Moderators were evaluated by testing the effect of time\*treatment condition\*exposure process variables. Models were built iteratively, with each predictor-moderator pair being included in its own model and evaluated for improvement in model fit as indicated by significant

reductions in -2Log Likelihood statistics and/or reduction in Akaike information criterion (AIC) and Bayesian information criterion (BIC) fit statistics. If they were not significant and did not improve model fit, they were not included in subsequent models.

Including missing data from patients who dropped out prematurely, 12% of provocation-specific data and 10% of Y-BOCS ratings were missing. Data were determined to be not missing completely at random using Little's test ( $\chi^2 = 574.6, p = .002$ ); accordingly, a maximum likelihood estimation approach was used to estimate missing data.

### 3. Results

#### 3.1. Sample description

The majority of the sample identified as White (84%) and a slight majority were male (59%). Mean age was 39 years. Please see Table 1 for a more complete summary of sample characteristics. There were no significant differences in age, gender, Y-BOCS, or depression severity across treatment groups (Carimi et al., 2019). There were similarly no significant differences in any of the provocation characteristics evaluated in this study across active and sham groups ( $ds < 0.24$ ;  $ps > .26$ ).

#### 3.2. Description of provocation characteristics

Thirty-five percent ( $n = 33$ ) of people did both "external" and "internal" provocations, whereas as 65% ( $n = 61$ ) only completed internal provocations. The mean number of provocations conducted was 3.6 ( $SD = 2.0$ ; range: 1–10). The mean SUDS distress rating during provocations was 6.0 ( $SD = 0.73$ ). Sample provocations are provided as part of the Appendix.

#### 3.3. Do exposure therapy processes predict or moderate treatment outcome?

##### 3.3.1. Post-treatment analyses

The MLM with the immediate post-treatment endpoint (week 6) is

**Table 1**  
Sample characteristics.

Male gender N (%)	55 (59%)
Age M (range)	38.8 (22.2–68.0)
Age of onset M (range)	13.1 (4–30)
Positive family history N (%)	53 (56%)
Baseline SDS M (SD)	19.4 (6.1)
Race	
White N (%)	78 (83%)
African American N (%)	4 (4%)
Asian	3 (3%)
Multiracial	2 (2%)
Native American	2 (2%)
South Asian	2 (2%)
Middle Eastern	2 (2%)
Arab	1 (1%)
Ethnicity	
Hispanic N (%)	6 (6%)
Baseline HDRS	
M (SD)	10.5 (5.6)
None N (%)	34 (36%)
Mild N (%)	44 (47%)
Moderate N (%)	15 (16%)
Severe N (%)	1 (1%)
Baseline Y-BOCS	
M (SD)	27.3 (4.0)
Moderate N (%)	33 (35%)
Moderate-Severe N (%)	54 (57%)
Severe N (%)	7 (7%)

Note: HDRS = Hamilton Rating Scale for Depression; SDS = Sheehan Disability Scale; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale. HDRS cutoffs are based on Zimmerman et al. (2013); Y-BOCS severity cutoff are based on Storch et al. (2015).

presented in Table 2. Although hierarchy progress was found to be a significant moderator in an initial model, adding this variable did not improve model fit and an inspection of the interaction effects did not reveal hierarchy progress as a differential predictor in sham vs. active groups (was non-significant in both; sham:  $b = 0.014, p = .66$ ; active Deep TMS:  $b = 0.018, p = .59$ ). Thus, it was excluded from further models. The following nested model showed a significant SUDS intensity\*time\*treatment condition interaction (see next section for three-way interaction interpretation). In the nested model that also controlled for between session habituation, there was also a main effect of distress during provocations, such that individuals who reported greater distress during provocations experienced less rapid symptom improvement through week 6 across sham and active groups.

##### 3.3.2. 4-Week follow-up analyses

The MLM is presented in Table 3. Only one exposure process variable was found to moderate Y-BOCS trajectories according to treatment group. Specifically, there was a significant SUDS intensity\*time\*treatment condition interaction.

To parse interactions, MLMs were re-run with subgroups. First, the effect of distress level on treatment outcome was investigated in both sham and active treatment groups, finding no effect of distress during provocations on treatment outcomes in sham,  $b = .21, p = .11$ , or active Deep TMS,  $b = -0.012, p = .92$ . Because this parsing method did not lead to a clear interpretation of the interaction effect, the sample was instead divided according to mean distress during provocations, dividing the sample into halves with higher vs. lower reported distress during provocations ( $M = 6.59, SD = 0.49$  vs.  $M = 5.43, SD = 0.36$ ). Symptom trajectories were then presented in sham and active groups for the higher half and subsequently the lower half to aid in interpretation of the significant interaction term. For participants who experienced lower distress during provocations, there was not a significant treatment group\*time interaction (i.e., no sham-active Deep TMS difference,  $b = -0.17, p = .35$ ), with active Deep TMS showing a predicted Y-BOCS decline of 7.2 and sham Deep TMS showing a predicted decline of 5.0. In contrast, those who reported higher distress during provocations experienced more rapid symptom reduction in active treatment (i.e., Deep TMS led to improved outcomes relative to sham,  $b = .34, p = .06$ ). Among those who experienced more distress during provocations, those in sham only experienced a 2.8 predicted Y-BOCS decline, while those in active Deep TMS showed a 5.4 predicted Y-BOCS decline on average. This difference is presented in Fig. 1.

The raw outcome data (rather than predicted scores as described in the previous paragraph) are also presented in Table 4 ( $M$  and  $SD$  at each assessment timepoint) and Fig. 2 (Y-BOCS change scores at each follow-up visit), which show substantial differences in Y-BOCS change scores between active and sham among patients who experienced high distress, particularly through week 6, and less substantial differences between active and sham in the low distress group.

## 4. Discussion

The goal of this study was to investigate exposure therapy processes during symptom provocations done as pre-cursor to Deep TMS sessions in a randomized controlled trial for adults with OCD. Based on extensive exposure therapy research (Craske et al., 2008; Foa & McLean, 2016), we expected that participation in a greater variety of provocations, experiencing more distress during provocations, more variability in distress during provocations, and experiencing decreasing distress across provocations would all be associated with improved treatment outcomes regardless of treatment group (active vs. sham). We also evaluated whether effects would be more pronounced in active relative to sham treatment. Only peak distress during provocations emerged as a significant moderator of efficacy, as those who reported higher distress during exposure had a more robust Deep TMS response vs. sham responses, with participants in the sham stimulation condition who



**Table 2**  
Multilevel model predicting Y-BOCS through week 6 (immediately post-treatment).

	Unconditional Means Model	Model A (Linear growth model) <sup>c</sup>	Model B (Hierarchy Progress)	Model D (Fear Activation)	Model D (Between-Session Habituation)	Model E (Distress variability)
<b>Fixed Effects</b>						
Intercept	24.18***	27.04***	27.03***	27.03***	26.99***	26.878850
<b>Predictors<sup>a</sup></b>						
Time		-0.94***	-1.05***	-2.45**	-3.13***	-2.30
Hierarchy Progress			.022			
Mean peak distress during provocation				.25	0.37*	0.27
SUDS slope for each participant					1.38	
SD SUDS						-.36
<b>Moderators<sup>b</sup></b>						
Hierarchy Progress			-.071*			
Mean peak distress during provocation				-.070*	-.063*	0.056
SUDS slope for each participant					3.67	
SD SUDS						-1.16
<b>Random Effects</b>						
Residual	12.93***	7.43***	7.33***	7.44***	7.38***	7.46***
Intercept	14.67***	10.17***	10.49***	10.11***	9.35***	9.88***
Time		0.60***	.57***	0.51***	0.49***	.50***
<b>Fit Statistics</b>						
-2LL	2466.25	2329.54	2324.83	2320.74	2244.82	2302.18
AIC	2472.25	2339.54	2338.83	2334.74	2262.82	2320.18
BIC	2484.42	2359.81	2367.21	2363.12	2299.06	2356.60

<sup>+</sup> p < .07 \*p < .05, \*\*p < .01, \*\*\*p < .001.

Note: 2LL: -2 Log Likelihood; AIC: Akaike's Information Criterion; BIC: Schwarz's Bayesian Criterion; SUDS=Subjective units of distress scale; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

<sup>a</sup> Coefficients corresponding with predictor variables refer to a predictor\*linear time interaction term.

<sup>b</sup> Coefficients corresponding with moderator variables refer to a predictor\*linear time\*treatment group (sham vs. active Deep TMS) interaction term.

<sup>c</sup> Indicates there were significant improvements in -2LL compared with the previous model (p < .05).

**Table 3**  
Multilevel model predicting Y-BOCS at week 10.

	Unconditional Means Model	Model A (Linear growth model) <sup>c</sup>	Model B (Hierarchy Progress)	Model C (Fear Activation) <sup>c</sup>	Model D (Between-Session Habituation)	Model E (Distress variability)
<b>Fixed Effects</b>						
Intercept	24.36***	26.48***	26.47***	26.02***	25.95***	25.89***
<b>Predictors<sup>a</sup></b>						
Time		-.63***	-0.70***	-1.30***	-1.58***	-1.15*
Hierarchy Progress			0.015			
Mean peak distress during provocation				.12	.17	.14
SUDS slope for each participant					1.28	
SD SUDS						-.34
<b>Moderators<sup>b</sup></b>						
Hierarchy Progress			-0.037			
Mean peak distress during provocation				-.041*	-.037	.041
SUDS slope for each participant					1.52	-.78
SD SUDS						
<b>Random Effects</b>						
Residual	14.65***	7.73	7.71	8.35	8.29	8.35
Intercept	15.22***	11.47	11.63	11.85	11.27	11.78
Time		0.26	0.24	0.21	0.20	0.20
<b>Fit Statistics</b>						
-2LL	3501.60	3252.00	3248.57	2785.82	2705.51	2764.94
AIC	3507.60	3262.00	3262.57	2799.82	2723.51	2782.94
BIC	3520.79	3283.99	3293.35	2829.41	2761.32	2820.93

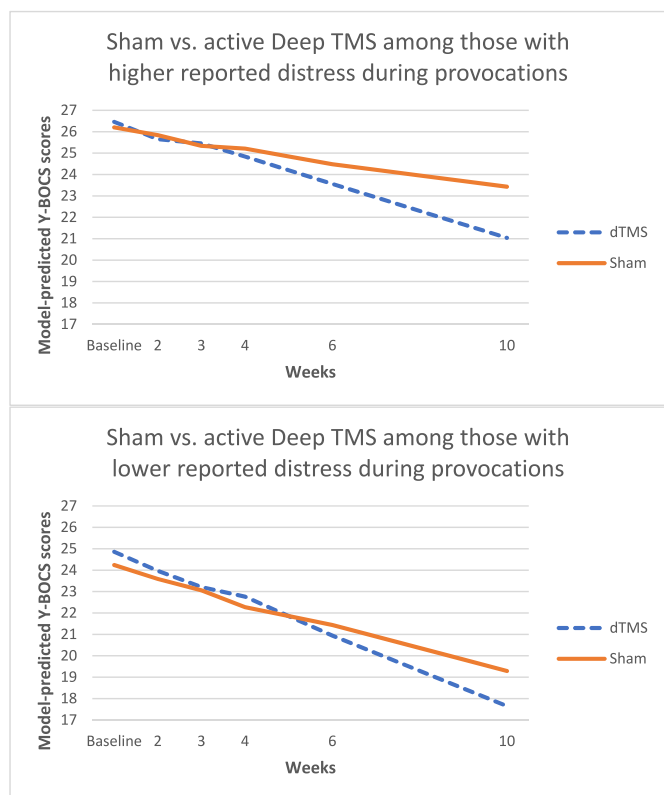
\*p < .05, \*\*p < .01, \*\*\*p < .001.

Note: 2LL: -2 Log Likelihood; AIC: Akaike's Information Criterion; BIC: Schwarz's Bayesian Criterion; SUDS=Subjective units of distress scale; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

<sup>a</sup> Coefficients corresponding with predictor variables refer to a predictor\*linear time interaction term.

<sup>b</sup> Coefficients corresponding with moderator variables refer to a predictor\*linear time\*treatment group (sham vs. active Deep TMS) interaction term.

<sup>c</sup> Indicates there were significant improvements in -2LL compared with the previous model (p < .05).



**Fig. 1.** Effect of distress during provocations on active vs. sham Deep TMS efficacy.

Note: TMS = Transcranial Magnetic Stimulation; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale.

**Table 4**

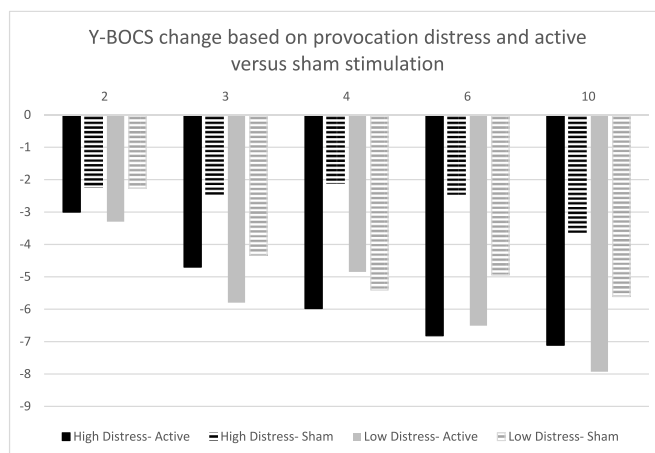
Y-BOCS scores at each follow-up point parsed by treatment group and emotional engagement during provocations.

	Baseline M (SD)	Week 2 M (SD)	Week 3 M (SD)	Week 4 M (SD)	Week 6 M (SD)	Week 10 M (SD)
<b>High distress during provocations</b>						
Active	29.29 (3.69)	26.29 (3.89)	24.59 (5.50)	23.31 (4.51)	22.47 (5.67)	22.18 (6.46)
Sham	27.25 (4.54)	25.00 (4.57)	24.75 (4.34)	25.13 (5.59)	24.8 (5.78)	23.64 (5.95)
<b>Low distress during provocations</b>						
Active	26.80 (3.92)	23.50 (4.43)	21.00 (4.71)	21.95 (5.24)	20.29 (4.62)	18.87 (5.54)
Sham	25.94 (3.59)	23.67 (3.24)	21.61 (4.08)	20.53 (5.56)	21.00 (5.91)	20.33 (6.59)

Note: Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

experienced high distress during provocations appearing to have the poorest treatment outcomes. None of the other exposure process variables were associated with treatment outcomes.

It is worth noting that significant symptom reduction was observed in both sham and active Deep TMS among those with less reported distress during provocation (5.0 and 7.2 point Y-BOCS decline respectively based on population-predicted models), though minimal symptom reduction was observed in the sham group among those with high distress during provocations (2.8 Y-BOCS decline; see Fig. 1 in which the flattest symptom change trajectories appears to be for individuals with high distress during provocations in the sham condition). Thus, high distress during provocations did not appear to lead to improved outcomes in terms of overall symptom reduction. It is possible that highly distressing provocations alone are insufficient for individuals with clinical OCD, and that modulation of CTSC circuits is only possible when



**Fig. 2.** Raw Y-BOCS change in active vs. sham stimulation among those who experience high vs. low distress during symptom provocations.

paired with further engagement of the mPFC or related areas (e.g., via neurostimulation). This seems to contrast with models of ERP that would suggest more distressing exposures would lead to improved outcomes, described as fear activation from an emotional processing perspective (Foa & McLean, 2016) or provoking feared expectancies in the inhibitory learning model (Craske et al., 2008). Together, this seems to point to differences between Deep TMS provocations and ERP exercises as described in more detail later in this discussion. It may be that those reporting higher SUDS ratings during provocations are simply those with more severe OCD, a sub-population that required active stimulation to achieve an efficacious response in a previous finding reported from this trial (Storch et al., 2021). This may also explain why higher mean distress was associated with faster symptom improvement at the six-week endpoint in a multivariate model controlling for between-session habituation (i.e., those with less severe symptoms reported lower distress during provocations). Alternatively, it may be that the improvement noted in sham for lower distress reflects a strong placebo effect, whereas the placebo effect washes out when participants also experience more distress during their daily treatments.

It is interesting to note continued linear improvement in symptoms through 4-week follow-up in the active arm among those with high distress, vs. minimal improvement through follow-up among those in sham (Fig. 1). This contrasts typical findings from exposure and response prevention trials, which usually show minimal change after acute treatment (e.g., Andersson et al., 2012; Foa et al., 2005). It may be that extinction learning continues beyond the end of acute Deep TMS treatment, and future research might investigate whether there is enhanced potential for neuroplasticity following a full course of neuromodulation treatment (i.e., is there an opportunity to optimize exposure and response prevention after TMS?).

Taken as a whole, however, this pattern of findings departs from our initial hypothesis that higher distress during provocations would lead to greater symptom reduction across conditions, potentially enhanced by active Deep TMS, as greater subjective distress would reflect greater activation of CTSC circuits and more pronounced corrective learning. Thus, although there was an improved active vs. sham response among those who experienced more distress, other hypotheses related to exposure processes leading to improved outcomes were not supported.

We believe there are several reasons this may be the case. Provocations differed from traditional exposures in some notable ways: 1) Exercises were designed to elicit subjective distress of 4–7 (out of 10) rather than the full range as is done in typical exposure; if some participants typically experienced distress at a level of 7–8, and others at 2–3, there may have been more variability to detect an effect of peak distress. 2) They were not conducted over a sustained period of time;

they were explicitly done to be brief enough so the participant would not have the opportunity to ritualize, whereas in exposure, obsessions are elicited over a prolonged period (i.e., up to 60 min or more) and patients are coached to resist compulsions despite a strong urge they may experience. 3) Provocations were designed to provoke doubt, which might challenge needs for certainty in many patients, but may not have tapped into specific feared expectancies (e.g., “I will stab someone if I hold this knife;” “I won’t be able to handle the feeling of my socks being uneven”). 4) Provocation hierarchies were followed stringently, beginning with the most approachable and moving up sequentially until distress of 4–7 was reached; in contemporary models of exposure, therapists move flexibly along a hierarchy and have the ability to alter goals to challenge obsessive fears (Knowles & Olatunji, 2019); this resulted in a mean of 3.6 different provocations being used per participant across the trial, which may have provided insufficient context variability in provocations (Craske et al., 2008). 5) Following provocations generated during the initial evaluation does not replicate the often creative and personalized “art” of exposure therapy (e.g., adapting location, props, proximity to trigger, etc., to personalize the exposure after initial hierarchy formation) 6) Post-exposure processing to enhance learning was not done as part of any of these sessions.

Future research may build on this work by investigating these processes during exposure therapy plus Deep TMS. Clinical trials investigating the potential of neuromodulation in bolstering exposure-based therapy have shown promising initial results (Nuñez et al., 2019); this research may continue to incorporate principles of exposure therapy (i.e., conducted over a sustained period; incorporating more variety into exposures; designed with violating feared expectancies in mind) and test whether exposure processes are associated with treatment outcomes.

Limitations from this study that should be noted. Foremost, the standardized design of provocations across participants likely prohibited statistical variability across participants needed to detect main effects (e.g., variability of distress experienced during exposure, minimal overall between-session habituation observed). That said, there was considerable variability in hierarchy progression and the number of provocation tasks attempted, though this variable did not prove to be a significant predictor or moderator as well. A larger sample would have provided the opportunity to detect significance with smaller effect sizes. Psychophysiological measures of distress during provocation would have provided an additional important measure of exposure processes as well. We are also limited in drawing firm conclusions about traditional exposure therapy plus noninvasive stimulation, as provocations differed considerably in several ways from exposure and response prevention exercises (e.g., the length of time conducted, the range of distress levels). Participants in this trial were enrolled primarily in North America, and thus results may not generalize to non-Western cultures. As is the case in post-hoc analyses like these, there is a risk that confounding factors could have accounted for results found here. There is also a risk of Type 1 error given the number of variables included in the models without statistical correction and modest overall effect sizes, and thus these preliminary observational findings should be followed up with replication and studies that experimentally manipulate these exposure process variables.

## 5. Conclusions

Results suggested that processes that are typically associated with treatment outcome during exposure therapy were not related to clinical improvement in a trial of symptom provocation plus Deep TMS vs. sham stimulation for adults with OCD. Future work should investigate the potential of exposure therapy combined with neurostimulation as an innovative, interdisciplinary way to enhance treatment outcomes.

## Author statement

**Andrew Guzick:** Conceptualization, methodology, formal analysis,

writing – original draft, visualization. **Ethan Schweissing:** Writing – original draft. **Aron Tendler:** Conceptualization, methodology, investigation, resources, writing – review & editing, supervision, project administration, funding acquisition. **Sameer Sheth:** Writing - review & editing. **Wayne Goodman:** Writing - review & editing. **Eric Storch:** Conceptualization, writing – review & editing, supervision.

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## Declaration of competing interest

Dr. Guzick receives funding from the Texas Higher Education Coordinating Board and the REAM Foundation/Misophonia Research Fund.

Dr. Aron Tendler has a financial interest and is the Chief Medical officer of BrainsWay, a clinical and research TMS center, as well as research support from BrainsWay, Liva Nova and Biohaven.

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Other authors have no declarations of competing interests to disclose.

## Data availability

Data will be made available on request.

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