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Neurofeedback for obsessive compulsive disorder: a randomized, double-blind trial

Mariela Rance[a,*], **Zhiying Zhao**[b,a,*], **Brian Zaboski**[c,&], **Stephen A. Kichuk**[c], **Emma Romaker**[a,c], **William N. Koller**[a], **Christopher Walsh**[a], **Cheyenne Harris-Starling**[a], **Suzanne Wasylink**[c], **Thomas Adams Jr.**[c,d], **Patricia Gruner**[c], **Christopher Pittenger**[c,e,f,g,#,@,&], **Michelle Hampson**[a,c,e,h,#,^]

[a]Department of Radiology and Biomedical Imaging, Yale School of Medicine

[b]Centre for Cognitive and Brain Sciences, University of Macau, Macau SAR, China

[c]Department of Psychiatry, Yale School of Medicine

[d]Department of Psychology, University of Kentucky

[e]Child Study Center, Yale School of Medicine

[f]Department of Psychology, Yale University

[g]Center for Brain and Mind Health, Yale School of Medicine

[h]Department of Biomedical Engineering, Yale School of Engineering and Applied Science

Abstract

We aim to develop fMRI neurofeedback as a treatment for obsessive compulsive disorder (OCD). In prior work, we found that providing neurofeedback of activity in the anterior prefrontal cortex (aPFC) improved control over contamination anxiety in a subclinical population. Here, we present the results of a randomized, double-blind clinical trial (NCT02206945) testing this intervention in patients with OCD. We recruited patients with primary symptoms in the fear-of-harm/checking or contamination/washing domains. During neurofeedback, they viewed symptom provocative images and attempted to up- and down-regulate the aPFC during different blocks of time. The active group received two sessions of neurofeedback and the control group received yoked sham

[#]corresponding authors: P.O. Box 208042, 1 Gilbert St, New Haven, CT 06520, 203-737-5994, michelle.hampson@yale.edu, Christopher.pittenger@yale.edu.

[*]These authors made an equal contribution

[#]These authors made an equal contribution

[^]Editor of *fMRI Neurofeedback*, Academic Press, London, 2021.

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feedback. The primary outcome measure was the Yale-Brown Obsessive-Compulsive Symptom scale. The secondary outcome was control over aPFC. Thirty-six participants completed feedback training (18 active, 18 control). The active group had a slightly but significantly greater reduction of obsessive-compulsive symptoms after neurofeedback compared to the control group ($p<0.05$) but no significant differences in control over the aPFC. These data demonstrate that neurofeedback targeting the aPFC can reduce symptoms in OCD. Future investigations should seek to optimize the training protocol to yield larger effects and to clarify the mechanism of action.

Keywords

neurofeedback; rt-fMRI; biofeedback; OCD; obsessive compulsive disorder

1. INTRODUCTION

New therapeutic interventions are needed for obsessive compulsive disorder (OCD) (Bloch et al., 2006; Jenike, 2004; Pallanti and Quercioli, 2006). Therefore, we developed a real-time fMRI neurofeedback protocol in which participants learn to control neural activity in a symptom relevant anterior prefrontal brain area (including frontal polar aspects of orbitofrontal cortex and Brodmann's area 10) during exposure to symptom-provocative images (Hampson et al., 2012; Scheinost et al., 2013; Scheinost et al., 2014). We tested this protocol on individuals with subclinical levels of contamination/washing OC symptoms and found a decrease in contamination anxiety and an increase in control over brain activity in the trained region (Scheinost et al., 2013). These promising results motivated a clinical trial in OCD patients with primary symptoms in the fear-of-harm/checking or contamination/washing domain. Here we report results from this double-blind, randomized trial (NCT02206945). Our primary hypothesis was that the neurofeedback from the aPFC area would improve OCD symptoms. A secondary hypothesis was that this training would improve participants' ability to control the target brain area, as measured in specific scans where participants were cued to increase and decrease activity in the target region without receiving feedback (hereafter referred to as *control task scans)*.

2. METHODS

The authors assert that all procedures contributed to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, revised in 2008. This study was conducted at Yale School of Medicine and the protocol was approved by the Yale Human Resources Protection Program (0206017435). All participants provided their written consent.

2.1 Participants

We enrolled individuals with OCD, 18 to 65 years of age, with a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)(Goodman et al., 1989a; Goodman et al., 1989b) score of at least 16 and primary symptoms in either the fear-of-harm/checking or contamination/washing domain (other symptoms were not exclusionary). All data were collected at Yale School of Medicine between July 2015 and November 2021. We recruited participants

through the Yale OCD Research Clinic (ocd.yale.edu) by advertising and community referrals; several different studies shared this same clinic recruitment stream, hence the large number of individuals screened. We established diagnoses using the MINI International Neuropsychiatric Interview 7.0(Sheehan et al., 1998) and confirmed them in a weekly consensus discussion with doctoral-level clinicians. Participants were either unmedicated or had been on a stable dose of an SSRI (or clomipramine) for at least 8 weeks, with no immediate plans to change their medication. Similarly, participants were either not receiving cognitive/behavioral therapy, or were in established maintenance therapy that had been ongoing for the past 3 months, with no immediate plans to change their therapeutic regimen. Exclusion criteria included active psychosis, autism spectrum disorder, a seizure disorder or other major neurological disorder, a history of major head trauma or psychosurgery, active substance abuse within the past 6 months, active suicidality, pregnancy, and severe claustrophobia. Psychotropic medication use was also exclusionary, except for stably dosed selective serotonin reuptake inhibitors or clomipramine, or a low-dose hypnotic or anxiolytic taken on an as-needed basis. (Hampson et al., 2012)

We invited consented participants for the first imaging session of the study, during which they underwent six localizer runs in which they viewed contamination or checking and neutral images in alternating blocks. After the scan, by contrasting the BOLD activity between two viewing conditions (symptom-related images > neutral images) using a voxel-wise generalized-linear model analysis in BioImage Suite (www.bioimagesuite.com) and an in-house script, we identified 30 voxels from aPFC that were most responsive to the provocative visual stimuli (Hampson et al., 2012). These 30 voxels became the individual target region for their neurofeedback training. If participants did not exhibit sufficient activation of the aPFC during the localizer task to define a target region, they were not randomized into the trial.

2.2. Trial Design

This was a double blind, sham-controlled, randomized trial. Participants and clinical assessors were blinded to group assignment. The CONSORT flow diagram is provided in the Supplementary Information, Figure S1.

The optimal number of sessions for fMRI neurofeedback applications is unknown. Typically, clinical applications use 2–3 training sessions: prior studies, both from our group (Scheinost et al., 2013; Sukhodolsky et al., 2020; Zhao et al., 2023) and other groups (Subramanian et al., 2011; Taschereau-Dumouchel et al., 2018; Young et al., 2017), have found this sufficient to induce symptom improvement. Our pilot study training down contamination anxiety in a subclinical population yielded very promising results with 2 sessions (Scheinost et al., 2013), therefore 2 sessions were used in this trial.

A yoked sham control was employed, meaning that each sham participant was shown the same feedback as a matched active participant, and given the same instructions at the same times. To the extent that the matched active participant was successful in controlling their brain activity, the sham participant was thus led to believe they were having the same level of success. We matched sham and active participants one-to-one, resulting in two groups that received the same amount of feedback indicating success in controlling their brain patterns.

We told participants that they might be randomized to a control feedback condition that we did not believe had the potential to help symptoms, but did not tell them the details of the yoked-sham procedure.

Using a computer program with a random number generator, we created two randomization lists prior to study initiation, one for participants with primary fear-of-harm/checking symptoms and one for participants with primary contamination/washing symptoms. Yoking of participants was always within the same list. A research staff member, who was not involved in the outcomes assessment, assigned participants based on the randomization list specific to the primary symptom dimension of that patient. There were separate provocative image sets for the contamination/washing and fear-of-harm/checking protocols that were developed and balanced in a similar manner, as described in detail in the Supplement. Researchers interested in using these stimuli should contact the corresponding author.

The yoked sham control requires that each sham control participant recruited be matched to a unique active experimental participant who preceded them in the study. Therefore, we created two randomization lists such that in each list the number of control participants at no time exceeded the number of active participants. When participants withdrew from the study, we assigned empty slots in the randomization lists to new participants. For a more detailed discussion on handling randomization in the context of a yoked sham control group, please see Hampson and Linden (2021).

2.3 Protocol

The intervention involved two feedback sessions, typically scheduled half a week apart. During these sessions, participants in the active group received feedback signal from the 30 voxels in the aPFC identified in the localizer session. Visual images were used to provoke symptoms during feedback, as in our pilot work; training control over aPFC activity in the context of pictorial symptom provocation may increase the congruence between the learning context and real-life situations in which patients struggle with *in vivo* symptom provocation. By creating a congruent learning context, we hoped to optimize translation into real-life clinical benefit. See below *Neuroimaging procedures* for details of the neurofeedback task and Supplement for calculation of feedback signal.

We conducted both clinical and neuroimaging assessments 2–7 days before the feedback sessions and 2–7 days after. We also collected clinical assessments at two weeks and one month after the feedback sessions. Thus, we collected clinical assessments at a total of four time points (baseline, a half-week post-training, 2 weeks post-training and one-month post-training), while we collected neuroimaging assessment sessions at two time points (baseline and a half-week post-training).

Prior to the first neuroimaging assessment session, participants from both groups met with a clinical psychologist from the Yale OCD Research Clinic who specialized in anxiety disorders. The goal of this visit was to help participants to develop individualized cognitive strategies that might provide some initial control over the brain activity when instructed to perform self-regulation during the following imaging sessions (Hampson et al., 2012).

2.3.1 Clinical assessments—Baseline and post-intervention clinical assessments included the Y-BOCS and adverse events screening. Because we anticipated that symptom change might be specific to the symptom domain targeted during neurofeedback, we performed the Y-BOCS twice at every timepoint: once across all OCD symptoms (the standard approach), and once specifically asking about the targeted symptom domain (contamination/washing or fear-of-harm/checking). All assessments were conducted by an experienced evaluator who was not involved in administering the intervention and was blind to participant group assignment. Some follow-up evaluations were conducted remotely, especially after the onset of the COVID pandemic.

2.3.2 Neuroimaging procedures—We used Siemens scanners (Siemens Medical Systems, Erlangen, Germany). The trial began on a Siemens 1.5T MAGNETOM Sonata scanner. Our center decommissioned this system midway through the trial and the study was shifted to a Siemens 3T MAGNETOM Prisma Fit system. All yoked control participants underwent neurofeedback on the same scanner as the active participant with whom they were matched; no participants switched scanner midway through the protocol. Details on the scanning parameters and types of scans collected are provided in the Supplement.

In the feedback runs, an arrow cued participants to rest, increase, or decrease activity in their target brain area and an image was shown (provocative in increase and decrease blocks and neutral in resting blocks). The feedback was provided in a line graph at the bottom of the screen (shown in Figure 1). To assess control before and after feedback, similar scans, without the feedback at the bottom, were used – these are referred to as control task scans.

The scanning protocol involved four sessions scheduled at half week intervals:

1. Baseline session with localizer: high-resolution structural scans; resting-state scans; control task scans; 5–6 localizer runs. We only invited participants to continue with the study (and randomized them) if the localizer successfully identified symptom provocation related activity in the aPFC region.
2. First neurofeedback session: 6 neurofeedback or yoked sham runs.
3. Second neurofeedback session: 6 neurofeedback or yoked sham runs.
4. Post-neurofeedback session: resting-state runs; control task.

2.3.3 Final debriefing sessions—After they completed all the clinical follow-ups, participants received an unstructured debriefing session, in which we asked whether they believed they received veridical or sham neurofeedback prior to unblinding them.

2.4 Data Analyses

2.4.1 Symptom change—The primary outcome measure was change in total Y-BOCS score over time following neurofeedback vs. yoked sham feedback. As the intervention targeted brain activity associated with the primary symptom dimension (fear-of-harm/checking or contamination/washing), we also examined a modified version of the Y-BOCS that queried specifically about symptoms along the primary symptom dimension (referred

to hereafter as “symptom-specific Y-BOCS”) to examine whether this was more sensitive to symptom change.

Details of the statistical analyses and tools used for visualizing the results are provided in the Supplement. In brief, for both total Y-BOCS and symptom-specific Y-BOCS scores, a mixed model was run that included a random intercept for participant, a fixed covariate for baseline, and a baseline by time interaction to control for baseline variance, dropout, and regression to the mean (Schuler, 2022; Senn, 2006). Next, to account for scanner effects over time across groups, we included parameter estimates for group (active vs sham neurofeedback), scanner (1.5 vs 3.0 Tesla), and time (3 sessions; modeled as a continuous variable), along with a four-way interaction term (baseline*group*time*scanner). After finding that the interaction term was non-significant, we then tested our primary model of interest. This model included a random intercept for participant, a fixed covariate for baseline and a baseline x time interaction term, and group, time, and group*time effects.

We used post-hoc t-tests to examine differences in total Y-BOCS scores between the treatment groups at each time point and Kenward-Roger degrees of freedom approximation to account for multiple comparisons.

2.4.2 Neuroimaging data—Our secondary outcome measure was change in control over the aPFC target region in the control task runs collected before and after training. This measures participants’ capacity to self-regulate in the absence of neurofeedback (these are referred as “transfer runs” in some neurofeedback literature). We calculated control over the target region at each timepoint as the GLM estimated activation differences between the up-regulation and down-regulation blocks during control task runs, averaged across all voxels in the target region. We computed one measure of control over the target region at baseline and one measure at the post-intervention time point for each participant. We then modeled pre-post target control differences using an ANCOVA with the dependent variable as post neurofeedback target control and baseline target control and treatment group as covariates (Wan, 2020).

Lastly, an exploratory analysis examined how control over the target region changed during neurofeedback sessions. Change in extracted beta-estimates averaged within the trained aPFC region in the up-regulate blocks relative to the down-regulate blocks was extracted for each feedback run of each participant and averaged across runs for an estimate of how well each participant controlled the target region during the training. We used a pooled t-test to compare control during training in the active and control groups.

3. RESULTS

3.1 Group baseline characteristics

The Yale OCD Research Clinic screens participants for multiple studies and routes participants based on our inclusion and exclusion criteria. Of 254 participants screened at the clinic, 45 met the criteria, were willing to participate, and were thus consented for this study, and 36 completed the intervention and follow-up (see Figure S1 for details). Table 1 displays the baseline demographic and clinical characteristics of the $N = 36$ completers.

3.2 Clinical change

Mixed model analysis revealed a statistically significant group*time interaction effect on Y-BOCS total score (p = .04); inspection of group means suggest that linear change in Y-BOCS total scores across the four assessments was greater for participants who received active neurofeedback group than for those who received sham neurofeedback (show in Figure 2). Post-hoc t-tests between groups were not significantly different at any individual time point, after controlling for multiple comparisons (p-corr. > .05, see Figure 2). Given that the randomization resulted in two groups that were not well-matched for age, we repeated these analyses including age as a covariate in the model. The group*time interaction effect was still significant (p=.04). The group effect was still not significant at any time point when controlling for age.

We also analyzed symptom specific Y-BOCS scores, but the group*time interaction for this measure did not reach significance (p = 0.26).

Further details of these analyses are provided in the Supplement.

3.3. Control Task Analysis

Results from the ANCOVA did not show a significant main effect of group on post-feedback control after accounting for individual baseline (p = 0.60).

3.4 Exploratory analysis of group differences in control during training

There were no significant group differences in participants' control over the target region as assessed during the training runs (i.e., in the presence of feedback).

3.5 Data from debriefing and adverse events monitoring

Debriefing data querying what intervention participants believed they received were available for 8 participants in each group. The majority of these (regardless of group) reported believing they received the active experimental intervention (6/8 in the sham group and 7/8 in the neurofeedback group). There were no adverse events related to the intervention.

4. DISCUSSION

This randomized clinical trial represents one of the largest real-time fMRI neurofeedback clinical trials to date, and the first in patients with OCD. We enrolled OCD patients who had primary symptoms in the fear-of-harm/checking or contamination/washing domains. The active intervention involved two sessions of neurofeedback targeting an individualized region in the anterior prefrontal area, functionally identified prior to neurofeedback using symptom provocation. Participants tolerated the intervention well (with only two dropping out after beginning the intervention, both for reasons unrelated to the study), and there were no adverse events related to the intervention. A statistically significant reduction in symptoms in the active group relative to the control group emerged over time, suggesting that this intervention has the potential to reduce symptoms in patients with fear-of-harm/checking or contamination/washing OCD. However, the symptom reduction was small,

with the maximum difference between groups being just over two points on the Y-BOCS (see Figure 2). Note the improvement in symptoms in the active group developed over time after neurofeedback training was complete. Conversely, Y-BOCS reductions emerged and stabilized immediately after the intervention for participants who received sham neurofeedback. As we have previously discussed, this pattern of change has been seen in other neurofeedback studies and is important to consider when designing neurofeedback protocols (Rance et al., 2018). Moreover, if this pattern were to persist with the addition of more neurofeedback sessions, then differences between sham and active neurofeedback might become more pronounced by post-treatment.

Although results of this trial demonstrate that neurofeedback targeting the anterior prefrontal cortex may reduce OCD symptoms, the small change in symptoms found (approximately 14% improvement in the active group) indicates this intervention, in its current form, is not clinically useful. Thus, an important question is whether the intervention can be optimized to induce larger effects. Given that we were targeting the anterior prefrontal cortex, a region of high susceptibility artifact in MR imaging, optimizing the scan protocol to minimize artifacts may enhance efficacy. Smaller voxels could be used to reduce the susceptibility artifact by employing multiband imaging. Although multiband imaging increases the computational load for the real-time analysis, this is manageable if the multiband factor is modest. As the precise alignment of brain microstructure with the magnetic field impacts the BOLD signal, it may also be helpful to ensure head alignment within the scanner is consistent across scan days using a tool such as HALO (Zhao et al., 2022). This is particularly important for a region with high susceptibility artifact, as it might prevent susceptibility-induced distortion effects from throwing signal into different voxels on different days.

Another consideration is the target region. Achieving control over a target area involved in a mental phenomenon does not necessarily change control over the mental phenomenon. In studies by Rance et al. (Rance et al., 2014a; Rance et al., 2014b), participants learned control over pain-elicited brain activity in two regions, and were trained to control each of the two regions independently, and also to control the differential activity of the regions. This training did not influence perceived pain intensity or unpleasantness, possibly due to the distributed nature of involved brain regions in the perception of pain. However, the approach may be worth exploring for other applications, and future studies could target different or even multiple regions that are related to OCD simultaneously. Alternately, connectivity patterns, rather than activity patterns, could be targeted. Prior studies have shown promise of connectivity based neurofeedback for improving emotion regulation (Koush et al., 2017; Zhao et al., 2019). Given our previous observation that changes in the global connectivity in the anterior prefrontal area correlated with improvements in control over contamination anxiety after training (Scheinost et al., 2014), network properties may be another promising target for neurofeedback.

The symptom provocation approach could also be further optimized. Stimuli were optimized to provoke symptoms in a subclinical population, but patients with OCD often have idiosyncratic triggers, and individual patients responded variably to the different stimuli. As a result, much of the training may have occurred in the absence of symptom provocation,

thereby limiting its translation to real-life scenarios in which patients struggle to control their high levels of anxiety. Using personalized stimuli, rather than standardized stimulus sets, might enhance translation of neurofeedback training to clinically relevant situations. Of course, creating personalized stimuli for each participant is very effort intensive. A simpler alternative may be to cue patients to imagine symptom-provocative scenarios. Modifying the training protocol to encompass more personalized forms of symptom provocation would have the added benefit that OCD patients who do not have primary fear-of-harm/checking or contamination/washing symptoms could participate.

Improving our understanding of the mechanism of action of the intervention may lead to other avenues of optimization. We hypothesized that the intervention would improve control over neural activity in the target region. Our data could not confirm that the intervention acted via this mechanism. The secondary outcome measure, change in control over the target region in the control task runs, showed no improvements in control that were specific to the active group. In addition, an exploratory analysis of control during the neurofeedback training (that is, in the presence of feedback) found no greater control in the active than the control group.

These measures of control over the target region may be affected by the idiosyncratic responses of participants to provocative stimuli during the control task and the feedback runs. Stimuli that were designed to be matched across up and down regulate periods at the group level may have induced different levels of provocation in individual participants, adding substantial noise to our estimates of control over the target region. This is an additional reason to move away from the use of standardized image sets for provocation during training and assessment scans.

A multitude of other variables might impact efficacy of this intervention, including, for example, the number of training sessions, the spacing of the training sessions, and the motivational salience of the feedback interface. The latter may be optimized by the use of virtual reality feedback interfaces, or paying participants based on their performance in controlling brain activity.

Note that fMRI neurofeedback is a highly novel intervention at an early stage of development, not an optimized intervention that is ready for large, well-powered, multi-site trials. Thus, although the trial reported here is one of the largest published fMRI neurofeedback clinical trials to date, it is still underpowered to examine gender or sex effects, and thus it is unclear if the effect seen is gender specific. This limitation should be addressed in future trials.

In summary, the data from this study suggest that fMRI neurofeedback of the anterior prefrontal cortex may be helpful for reducing OCD symptoms, but that protocol optimization is needed. We highlight the need for optimization of the scanning protocol to minimize and stabilize susceptibility artifact in the target region, and optimization of the provocation paradigm to ensure dependable and consistent provocation in the patients during training.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Example screenshot from the end of a neurofeedback run. A white arrow pointing forward and neutral image are shown because the run ended on a resting block. During up- and down-regulate blocks, a red up-arrow and blue down-arrow were shown, respectively. During each regulate block, a provocative image was shown. The matched yoked sham participant saw the same display during their feedback run.

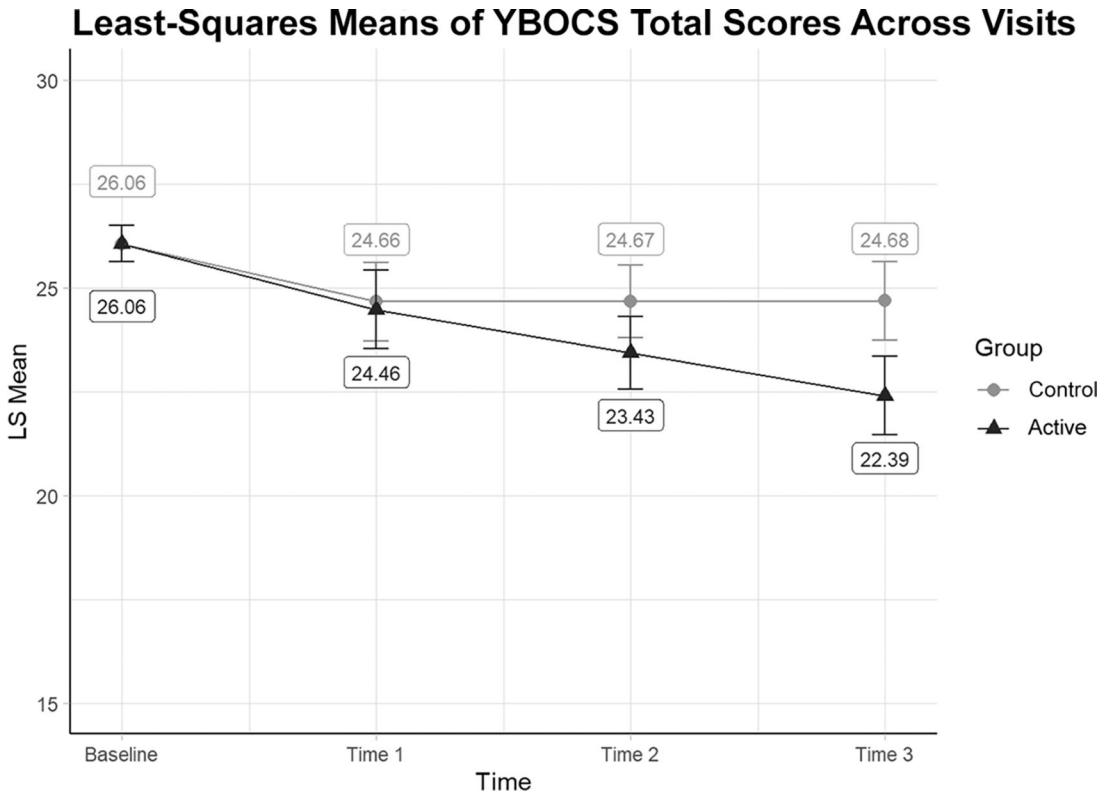

Fig 2.

Model Means and Standard Errors of Overall Y-BOCS Scores. The group*time interaction was significant (p = 0.04). Post-hoc test statistics were generated via the Kenward-Roger approximation. Alpha level was set to α = .05. Error bars represent standard error.

Table 1

Baseline Descriptive Statistics by Group

Demographic	Control				Treatment			
	n	**% Total**	***M***	***SD***	***n***	**% Total**	***M***	***SD***
Age	18	100	31.4	8.64	18	100	40.10	13.80
Gender (Female)	12	67	-	-	13	72	-	-
Y-BOCS Total	18	100	25.30	4.31	18	100	26.80	4.92
Education (years)	18	100	14.72	2.27	18	100	14.28	2.30
Psychiatric Comorbidity	8	44	-	-	8	44	-	-
MDD	4	22	-	-	6	33	-	-
PTSDs	2	11	-	-	2	11	-	-
Anxiety disorder	4	22	-	-	3	17	-	-
OCRD	1	6	-	-	0	0	-	-
Eating disorder	1	6	-	-	1	6	-	-
Psychoactive medication	7	39	-	-	5	28	-	-
SSRI	6	33	-	-	3	17	-	-
Clomipramine	1	6	-	-	0	0	-	-
As-needed sleep medication	0	0	-	-	1	6	-	-
Thyroid hormone	1	6	-	-	1	6	-	-
Cabergoline	1	6	-	-	0	0	-	-

Note: N = 36 participants randomized. MDD – Major Depressive Disorder; PTSD – Post-traumatic stress disorder; OCRD – obsessive-compulsive related disorder; SSRI – selective serotonin reuptake inhibitor