EXPOSURE-RESPONSE PREVENTION, EXECUTIVE FUNCTION, AND BRAIN ACTIVATION IN PARTICIPANTS WITH OBSESSIVE-COMPULSIVE DISORDER

BY

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THESIS

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ABSTRACT

Background: Obsessive-Compulsive Disorder (OCD) is a highly impairing disorder that has been linked to executive function (EF) deficits, particularly in the domains of response inhibition and emotion regulation. Both domains are associated with brain regions that have dysfunctional activation in OCD populations. Exposure-response prevention therapy (ERP) is the most effective and utilized treatment for OCD, but little is known about the relationship between ERP and EF-related brain activation. **Methods:** Inpatients in a residential OCD treatment facility (n=11) completed two MRI scans, one upon admission to the program and one after a month of treatment in the program. An emotional Stroop and a stop-signal task were administered during scans to investigate changes in brain activation pre- and post-treatment. In addition, a resting state was conducted during both scans. Clinician-administered questionnaires assessing OCD and depression severity were conducted at both visits. **Results:** Brain activation results did not show any significant changes in regions of interest related to the emotional Stroop or stop-signal task. Exploratory functional connectivity analysis of the resting state data using regions either associated with OCD symptoms (default mode network regions & amygdala) or general treatment response (anterior cingulate cortex & frontal orbital cortex) revealed alterations in functional connectivity pre- and post-treatment. **Conclusions:** Present results support the need for further exploration into neurological processes associated with OCD treatment and identify amygdala, anterior cingulate cortex, frontal orbital cortex, and default mode network regions as areas of interest in OCD functional connectivity. Results also provide further information about the relationship between EFs and treatment response.

Keywords: OCD, ERP, Executive Function, Response Inhibition, Emotion Regulation, Resting State

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental health disorder characterized by the presence of intrusive and perseverative thought patterns known as obsessions and/or the engagement in repetitive behaviors to regulate distress, referred to as compulsions (American Psychiatric Association, 2013). In most cases of OCD, both dimensions are present and are related in that obsessions cause distress for an affected individual, who then engages in ritualistic compulsions to reduce that distress (Abramowitz, 1998).

Individuals with OCD symptoms demonstrate severe impairment and experience detrimental effects to their quality of life (Eisen, et al., 2006; Ruscio, Stein, Chiu, & Kessler, 2010). This degree of impairment is often related to the severity of the symptom presentation, which is commonly calculated by the amount of time spent each day engaging in obsessions and compulsions and the amount of distress experienced (Abramowitz, 1998; Grabill, et al., 2008). Other factors, such as a person's age of onset, insight into their condition, and the presence of comorbid disorders, also affect the severity of and difficulties encountered due to OCD (Graybiel & Rauch, 2000; Saxena, et al., 2001; Ruscio, Stein, Chiu, & Kessler, 2010). While individuals with an OCD diagnosis often seek treatment, only one third receive treatment specifically developed to treat the disorder (Ruscio, Stein, Chiu, & Kessler, 2010).

Exposure-Response Prevention Therapy

Given that many individuals are unable to receive treatment specifically designed to treat OCD, it is important to examine what effective treatment looks like for this population. Exposure-response prevention (ERP) therapy is considered the gold standard in OCD treatment and has strong research support for its effectiveness in reducing obsessions and compulsions (Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000; Abramowitz, Franklin, & Foa, 2002; Eddy,

Dutra, Bradley, & Westen, 2004; Fisher & Wells, 2005; Foa, et al., 2005). Despite its efficacy, complete alleviation of symptoms is uncommon in a clinical population (Abramowitz, 1998; Fisher & Wells, 2005). The chronic nature of OCD and the continuation of subclinical symptoms after treatment provides further reason for providing clarification as to the factors that impact its effectiveness.

Exposure-response prevention therapy works by systematically exposing individuals to situations that trigger their obsessions and preventing them from using compulsions to reduce that distress (Abramowitz, 1998; Freeston & Ladouceur, 1999). While ERP is considered a predominantly behavioral intervention, it also utilizes cognitive reappraisal and restructuring as a primary part of the desensitization process (Abramowitz, 1997; Abramowitz, Franklin, & Foa, 2002; Huppert & Roth, 2003). In addition to immediate effectiveness in reducing symptoms, symptom improvements after ERP remain stable over longer periods of time (Rufer, et al., 2005; Fisher & Wells, 2005).

Executive Functions

Given that OCD leads to significant impairment and has a preferred treatment which utilizes cognitive-behavioral methods, there is interest in looking at specific executive functions (EFs) within this population to examine how they relate to treatment response and symptom improvement. EFs are higher order cognitive mechanisms used to engage in goal-oriented behavior and have been found to be a general predictor of OCD treatment effectiveness (Hamatani, et al., 2020). Within the OCD research literature, the most commonly studied domains of EF include attention, planning, working memory, inhibition, shifting, verbal, and nonverbal abilities.

Executive function deficits have been identified within clinical and subclinical OCD populations (Gillan, et al., 2011; Abramovitch, Dar, Schweiger, & Hermesh, 2011; Kashyap, Kumar, Kandavel, & Reddy, 2013; Millet, et al., 2013; Snyder, Kaiser, Warren, & Heller, 2015). Given that these difficulties extend into a subclinical population, it is important to determine specifically how these potential deficits may interact with the effectiveness of treatment outcomes. In addition, these findings can be difficult to interpret due to smaller effect sizes, smaller sample sizes, inconsistent replication, the transdiagnostic nature of EFs, and non-causal analyses (Kuelz, Hohagen, & Voderholzer, 2004; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Abramovitch & Abramowitz, 2014; Abramovitch, Shaham, Levin, Bar-Hen, & Schweiger, 2015). Examining more constrained domains of EF may help to address some of these concerns by narrowing some of the task and construct diversity that accompanies broader measures of EF.

Inhibition

Inhibition, often divided into cognitive and motoric dimensions, is a domain of EF consistently demonstrated to be dysfunctional in populations with OCD (Bannon, Gonsalvez, Croft, & Boyce, 2002; Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Bannon, Gonsalvez, & Croft, 2008; Menzies, et al., 2008; Lei, et al., 2017; Hu, et al., 2020; Mar, Townes, Pechlivanoglou, Arnold, & Schachar, 2022). Given this prevalence, it is probable that individuals seeking treatment for OCD will have difficulties with this EF domain.

Cognitive inhibition encompasses the ability to delay gratification and prevent unwanted thoughts or emotions (Logan & Cowan, 1984; Bechara, Damasio, & Damasio, 2000; McLaughlin, et al., 2016), while motoric inhibition involves the ability to prevent or disengage from an initiated physical action, often in response to a change in the environment (Logan &

Cowan, 1984; Nigg, 2000). Regardless of type, effective inhibition also requires appropriate context-monitoring to determine the appropriateness of actions or thoughts in a situation (Nigg, 2000; Chatham, et al., 2012). While inhibition findings are robust in the literature, it is important to note some studies were unable to replicate inhibition deficits, with task sensitivity being a potential concern (Bohne, Savage, Deckersbach, Keuthen, & Wilhelm, 2008; Kalanthroff, et al., 2017; Rosa-Alcazar, et al., 2020).

To measure inhibition in OCD, tasks such as the stop-signal task, which instructs participants to cancel a previously engaged behavior, are often used (Logan & Cowan, 1984; Verbruggen & Logan, 2008). While these behavioral tasks primarily measure motor inhibition, they are also indirect measurements of cognitive inhibition and context monitoring (Chatham, et al., 2012; Mar, Townes, Pechlivanoglou, Arnold, & Schachar, 2022). This ability to tap into the three dimensions of inhibition makes the stop-signal task an excellent methodological choice for operationalizing response inhibition.

Neuroimaging activation studies have examined inhibition both in healthy control and OCD populations in the interest of examining regions of the brain involved in muscle movements, salient event processing, and response selection as part of a larger inhibition processing network. A commonly identified area of the brain involved in inhibition processing, particularly with regards to suppressing motoric movements, is inferior frontal gyrus (IFG) (Rubia, Smith, Brammer, & Taylor, 2003; Aron, Robbins, & Poldrack, 2004; Chamberlain & Sahakian, 2007; Verbruggen & Logan, 2008; Aron R., 2011; Sebastian, et al., 2013). Dysfunctional activation in this primary hub of inhibition has been indicated in OCD (Roth, et al., 2007; de Wit et al., 2012). Another area of inhibition associated with suppressing motoric

demands is subthalamic nucleus, which occasionally has been linked to altered activation in OCD (Aron & Poldrack, 2006; Aron R., 2011; Chatham, et al., 2012).

With regards to salient event processing, anterior cingulate cortex (ACC), anterior insula, and parietal cortices are theorized to provide context monitoring and selective attention during inhibition. ACC activation occurs during cognitively demanding tasks and error monitoring, and as a region it has exhibited altered activation patterns in OCD during inhibition-related behavioral tasks (Bush, Luu, & Posner, 2000; Menzies, et al., 2008; Kang, et al., 2013; Norman, et al., 2019). Anterior insula is another location involved in the processing of salient events that shows dysfunctional activation in OCD during inhibition tasks (Swick, Ashley, & Turken, 2011; Chatham, et al., 2012; Sebastian, et al., 2013; Norman, et al., 2019). Taken together, this research provides evidence that altered attention and context monitoring may lead to impaired inhibition in an OCD population. Additionally, regions of the brain such as parietal cortex engage in context monitoring focused on errors, as its activation patterns have been linked to moments of failed inhibition (Rubia, Smith, Brammer, & Taylor, 2003; de Wit, et al., 2012; Kang, et al., 2013; Sebastian, et al., 2013).

Pre-supplemental motor area (pSMA) also plays an important role in inhibitory processes by aiding with response selection and action cancelation, a form of motoric inhibition (Aron & Poldrack, 2006; Verbruggen & Logan, 2008; Aron R., 2011; Chatham, et al., 2012; Sebastian, et al., 2013). Consistent with prior research on this topic, pre-SMA also shows dysfunctional activation in OCD populations (de Wit, et al., 2012; Norman, et al., 2019).

Given observed patterns of altered activation in OCD across regions of the brain associated with inhibition, it is possible these regions are involved in the severity of OCD symptoms. By that premise, individuals undergoing treatment to reduce the severity of their

OCD symptoms may also see changes in the activation of these regions. If there are changes in activation across these regions as well as changes in behavioral measures of inhibition before and after treatment, it provides evidence that ERP treatment impacts inhibitory capabilities in OCD.

Emotion Regulation

Aspects of emotion regulation, another EF domain, also show impairment in people with OCD (Fergus & Bardeen, 2014; Stern, Nota, Heimberg, Holaway, & Coles, 2014; Berman, Shaw, & Wilhelm, 2018; Yap, et al., 2018; Eichholz, et al., 2020; Khosravani, Ardestani, Bastan, & Malayeri, 2020). Being able to identify and understand one's emotional experiences, along with appropriate use of emotion regulation strategies, are both aspects of emotion regulation that prior research has identified as greatly impaired in OCD (Fergus & Bardeen, 2014; Stern, Nota, Heimberg, Holaway, & Coles, 2014; Berman, Shaw, & Wilhelm, 2018; Khosravani, Ardestani, Bastan, & Malayeri, 2020).

Ameliorating distress caused by negative cognitions by using maladaptive repetitive behaviors is a hallmark feature of OCD, suggesting that a deficit in emotion regulation is fundamental to the conceptualization of this disorder. Expressive suppression, a strategy which involves altering or disengaging from behavioral expressions of emotion, is frequently utilized by those who have OCD and has been linked to symptom severity (Fergus & Bardeen, 2014; Goldberg, et al., 2016; Khosravani, Ardestani, Bastan, & Malayeri, 2020). Comparatively, the use of beneficial emotion regulation strategies such as cognitive reappraisal, which encourages situation reinterpretation, is less frequently utilized by individuals with OCD. (Stern, Nota, Heimberg, Holaway, & Coles, 2014; Goldberg, et al., 2016; Paul, Simon, Endrass, & Kathmann, 2016). Since the most recommended treatment for OCD is ERP, a type of cognitive-behavioral therapy that uses cognitive reappraisal, problems with deploying this strategy could have a

negative impact on treatment efficacy. Some research studies have indicated that emotion regulation skills enhance the ability to engage with cognitive reappraisal and ERP, leading to improvements in therapeutic outcomes (Fergus & Bardeen, 2014; Yap, et al., 2018; Khosravani, Ardestani, Bastan, & Malayeri, 2020). To elucidate why or why not treatment is effective for a population, it is important to explore how factors such as emotion regulation ability impact treatment success and symptom improvement.

Given that the improvement of emotion regulation strategies in OCD is linked to treatment outcomes, it is important to explore whether regions of the brain involved in emotion regulation processes show changes in activation during the treatment process. Since emotion regulation has been conceptualized as an interaction between emotion perception and emotion conflict, it is essential to examine regions of the brain associated with these processes. Like other complex behaviors, emotion regulation involves multiple brain regions functioning together as part of a larger regulatory network. Of these regions, activation in amygdala is frequently studied due to its association with the initial perception of and responsiveness towards salient emotional stimuli, particularly if the stimuli is perceived as threatening (Taylor & Liberzon, 2007; Ochsner, Silvers, & Buhle, 2012). When studies assessing symptom provocation and emotion regulation in OCD are conducted, alterations in amygdala activation have been found in OCD in comparison to healthy control populations (Brennan, et al., 2015; de Wit, et al., 2015).

After an emotional stimulus is identified, activation occurs in areas of the brain that engage in emotion conflict monitoring. Among these areas, dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), and ACC are involved in different aspects of conflict monitoring (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Taylor & Liberzon, 2007; Ochsner, Silvers, & Buhle, 2012). Activation in dmPFC has been observed on tasks requiring

mental state inference, while dlPFC activates during periods of conflict resolution and cognitive reappraisal (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Ochsner, Silvers, & Buhle, 2012). These areas also demonstrate altered activation for OCD populations during tasks of emotion regulation (de Wit, et al., 2015). ACC, particularly rostral ACC, demonstrates a similar pattern in that its activation is linked to periods of conflict resolution, and it displays different activation patterns in OCD populations (Brennan, et al., 2015; de Wit, et al., 2015; Weidt, et al., 2016).

Regions of the brain associated with emotion regulation processes have shown different patterns of activation in OCD compared to healthy control populations. This is interesting considering prior research that individuals with OCD are more likely to use less effective emotion regulation strategies. Since ERP encourages the use of strategies such as cognitive reappraisal, emotion regulation skill development can be considered a potential therapeutic outcome. Exploring whether there are changes in activation across brain regions associated with emotion regulation before and after treatment provides evidence that changes in emotion regulation processing is an outcome of ERP.

Primary Hypothesis

Behavioral research has shown that individuals with OCD show impairments in inhibitory and emotion regulation abilities, while neuroimaging research conducted with OCD populations has identified altered brain activation in regions associated with both of those executive function domains. The primary purpose of this study is to determine whether the aforementioned regions associated with inhibition and emotion regulation show any differences in activation following a one-month course of intensive residential ERP. If there are activation changes, that suggests engaging in treatment correlates with changes in regions associated with executive functioning. Since the reduction of OCD symptoms during treatment is considered a

primary outcome, this study additionally explores whether changes in OCD symptoms correlate with activation alterations in these brain regions.

Exploratory Hypothesis

In addition to the primary hypothesis, a second exploratory analysis on functional connectivity was performed based on available connectivity literature that suggested individuals with OCD displayed altered functional connectivity in the default mode network (DMN; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012; Hou, et al., 2013) and amygdala, with additional studies reporting relationships between amygdala connectivity and responsiveness to CBT treatment (Pico-Perez, et al., 2019; Gao, et al., 2021; Cyr, et al., 2021). Two other regions, ACC and orbitofrontal cortex, were also included since prior research showed an association between changes in functional connectivity for these regions and general treatment response in individuals with psychopathology (Fettes, Schulze, & Downar, 2017; Liu, et al., 2022; Pico-Perez, et al., 2022). Given the increasing relevance of functional connectivity and the infrequency of pre-post treatment functional connectivity data for OCD, this exploratory analysis was conducted to examine changes in functional connectivity for these four regions before and after ERP.

METHODS

Procedure

All OCD participants were recruited from the Obsessive-Compulsive Disorders Institute (OCDI) at McLean Hospital, an intensive residential treatment program for severe OCD. Participants consented to a larger longitudinal database study run by the OCDI. As part of their participation in that database study, they completed a standard clinical evaluation which included the Structured Clinical Interview for DSM-IV Diagnoses (SCID-IV; American Psychiatric Association, 1994) and a self-administered Dimensional Obsessive-Compulsive Scale (DOCS). All participants gave prior consent to be contacted by the research team before being approached for participation in the current study.

All study procedures were approved by the McLean Hospital Institutional Review Board prior to recruitment. Participants approached for participation in the current study completed a pre-screening interview with the research coordinator, who assessed for eligibility. Inclusion criteria for the study included being between the ages of 18-65, having a DSM-IV diagnosis of OCD as their primary diagnosis, and having a score of at least 16 or higher on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Participants were excluded if they had a history of substance abuse or dependence (excluding nicotine) within three months of enrollment, a history of psychosis, a history of autism-spectrum disorder, any significant medical or neurological illness, a contraindication to MRI scanning, or pregnancy.

Participants who met eligibility and consented to the study were enrolled. The study involved two MRI sessions with a total involvement time of approximately 3.5 hours. The first MRI scan was performed within the first week of enrollment at the OCDI, and the second MRI scan was performed 4 weeks after the first scan.

Prior to each scan, a study investigator met with the participants and administered a brief demographic questionnaire, the Y-BOCS, and the Montgomery-Asberg Depression Rating Scale (MADRS). During the study, medication management was continued as part of participants' inpatient treatment, which occasionally created changes in medications between the two scans.

Directly before each scan participants completed brief practices of the tasks outside of the scanner to familiarize themselves with the instructions, and participants of childbearing potential completed a urine pregnancy test. Inside the scanner they completed a stop-signal task, an emotional Stroop task, and a resting state scan. At the end of the study participants were compensated for their time.

Participants

A total of 17 participants were enrolled in this study. Of those 17, 11 completed all study procedures with usable data (Table 1; Table 2). 1 participant was omitted due to being a pilot participant without OCD, 4 participants were omitted due to not being able to schedule a 2nd MRI scan within the follow-up timeframe, and 1 participant was omitted due to excessive head motion during the two MRI scans. The 4 participants omitted due to scheduling did not differ significantly from the included participants on any initial clinical measures. However, since outcome measures were determined by the change in OCD symptoms as measured by the clinician-administered Y-BOCS, it is not possible to determine if these participants differed in treatment response. The participant omitted for movement during the scans did not significantly differ from included participants on any clinical outcomes.

Scales

The following are scales that were either administered or analyzed as part of the study protocol.

Y-BOCS

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman, et al., 1989) is a 10-item clinician-administered questionnaire designed to assess the severity of obsessive-compulsive disorder symptoms. The Y-BOCS assesses the amount of time spent, the impairment in functioning experienced, the degree of distress, the resistance of, and the success in resistance of both obsessions and compulsions. Each item is scored from 0 to 4, with 0 indicating no observed symptoms and 4 indicated extreme symptoms. Cutoff points for this scale include: 0-7 indicating subclinical OCD symptoms, 8-15 indicating mild OCD symptoms, 16-23 indicating moderate OCD symptoms, 24-31 indicated severe OCD symptoms, and >31 indicating extreme OCD symptoms. In addition to the initial evaluation of OCD symptoms, the Y-BOCS has regularly been used as a pre-post measure to examine improvement in OCD symptoms.

Montgomery-Asberg Depression Rating Scale (MADRS)

The Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) is a 10-item clinician-administered questionnaire used to assess the severity of depressive symptoms, with higher scores indicating greater levels of depression. Specifically, the MADRS measures dimensions of sadness, physiological changes, apathy, pessimism, and suicidality. Each item has a rating scale of 0 to 6, with a possible range of 0-60. Cutoff points for this scale include: 0-6 indicating no significant depressive symptoms, 7-19 indicating mild depressive symptoms, 20-34 indicating moderate depressive symptoms, and >34 indicating severe depressive symptoms.

Dimensional Obsessive-Compulsive Scale (DOCS)

The Dimensional Obsessive-Compulsive Scale (DOCS; Abramowitz, et al., 2010) is a 20-item self-report measure that provides information about the severity of OCD symptoms among four symptom dimensions. The symptom categories included are concerns about germs and contamination, concerns about being responsible for harm, injury, or bad luck, unacceptable thoughts, and concerns about symmetry, completeness, or needing things to be "just right." Each dimension contains 5 questions assessing the amount of time spent on obsessions/compulsions, the avoidance towards a symptom, the distress and anxiety towards a symptom, the impairment due to obsessions/compulsions, and the ability to dismiss obsessions/compulsions.

Tasks

The stop-signal task was administered as a behavioral measure of inhibition, while the emotional Stroop task provided a behavioral measure of emotion regulation.

Stop-Signal Task

The stop-signal paradigm task code is identical to the task used in Chatham et al.'s 2012 paper, with the exception of code alterations made so the task could run inside of a scanner (Schneider, Eschman, & Zuccolotto, 2002). In this task participants were shown an arrow and instructed to press a button to indicate the direction the arrow was facing (either left or right), as fast and as accurately as possible. For some trials an additional stimulus (a white square) was presented at varying intervals following the onset of the arrow. On these trials, participants were instructed to try and stop their button response once the white square appeared, but were explicitly instructed to not slow down and wait for the square to appear. If the participant pressed a button while the white square was visible, it turned red. The task also includes null trials, in which an empty fixation ring is visible to the participant.

Of the 240 non-null trials, 75% were “No Signal Trials” and involved just the arrow. The other 25% of trials were “Stop Signal Trials,” which involved the square. The stop-signal response time (SSRT) and inhibition accuracy were behavioral variables of interest. In addition, onset times of task stimuli were used to compute contrasts during first-level activation analysis.

Emotional Stroop

The emotional Stroop paradigm is identical to the task used in Etkin et al.’s 2006 paper, with the exception of code alterations made so the task could run inside of a scanner (Schneider, Eschman, & Zuccolotto, 2002).The task consists of 148 presentations of happy or fearful faces with the words “HAPPY” or “FEAR” written in prominent red letters over the face. Participants were asked to identify the affect expressed on each face by pressing buttons on a button box corresponding to “fear” and “happy.” Stimuli were presented for 1000 milliseconds, with a varying inter-stimulus interval of 3000-5000 milliseconds during which a central fixation cross is shown.

Stimuli are coded as being either congruent (when the written word matches the facial affect shown) or incongruent (when the written word does not match the facial affect). Furthermore, incongruent stimuli are further divided into low conflict resolution (where an incronguent stimulus was preceded by a congruent stimulus) and high conflict resolution incongruent (where an incongruent stimulus was preceded by an incongruent stimulus). Overall response time and accuracy were behavioral variables of interest. Incongruent and congruent stimulus onset times were used to compute contrasts during first-level analysis analysis.

Brain image acquisition

All participants were scanned on a Siemens Trio scanner using a 32-chanel matrix coil and operating at a 3 Tesla magnetic field strength.

A field map was acquired to be applied to all functional imaging sequences. The parameters for the field map were: 66 slices, slice thickness 2.5 mm, TR 1250 ms, TE 1 10.0 ms, and TE 2 12.46 ms. The duration of the field map acquisition was two minutes and forty-four seconds.

All three functional sequences were acquired using a high-resolution multiband spin-echo EPI sequence employing a GRAPPA parallel imaging technique (TR/TE/flip angle = 720 ms/30 ms/66°). Additional parameters for these scans were: 66 transverse slices, slice thickness 2.5 mm, voxel size 2.5 x 2.5 x 2.5 mm, EPI factor 86, echo spacing 0.55 ms, interleaved excitation, phase encoding foot to head, and a multiband acceleration factor of 6. Prior to each scan, four images were acquired and discarded to allow for longitudinal magnetization to reach equilibrium.

The duration of the resting state run was ten minutes and twelve seconds, the duration of the stop-signal task run was eleven minutes and thirty-five seconds, and the duration of the emotional Stroop task was twelve minutes and thirty-seven seconds.

High resolution T1-weighted structural images were also collected. Parameters for the T1 were: 176 slices, slice thickness 1 mm, voxel size 1 x 1 x 1 mm, TR = 2530 ms, TI = 1100 ms, flip angle = 7°, TE 1 = 3.31 ms, and TE 2 = 6.99 ms. During acquisition the scanner console automatically combines the two images collected into a single root mean squared volume (RMS). The duration of the T1 acquisition was six minutes and three seconds.

Behavioral Data Analysis

The behavioral data was analyzed using R Studio (R Core Team, 2020). Task condition names, onset times, and event durations for task stimuli presentation were extracted for use in imaging preprocessing, while paired-sample t-tests were used to determine differences in task response times or accuracy in either the emotional Stroop or stop signal task.

Activation Imaging Analysis

All imaging data was preprocessed using the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm) running on MATLAB R2019a (MATLAB, 2019). To test for overall movement parameters, a realignment-only set of the functional data was run and framewise displacement (FD) was calculated using Power's guidelines and to prevent any movement correction due to slice timing preprocessing (Power, et al., 2014). All participant data with an average FD greater than 5 mm of movement was removed from analysis, with the exception of one participant who had values for the Stroop task below 5 mm of movement after the removal of outlier values. One participant was excluded for significant movement parameters (detailed under participants).

The preprocessing for the imaging data was conducted as follows: Using an extraction script, slice timing files for each functional run were created from participant json files. In SPM, slice timing correction was run on expanded 4D nii files with the scan parameters entered as appropriate in the settings. The slice timing files were entered under slice acquisition and the average timing was used as a reference slice as opposed to traditional interleaved parameters to account for the multiband acceleration factor. After slice timing correction, the field map data was created to account for inhomogeneities in the MRI field. The default parameters in SPM were then used to realign and unwarp the functional data using the previously calculated field

map. Afterwards, the T1 anatomical image was coregistered to the functional data and a deformation field was estimated. This deformation field was used to normalize the unwarped and slice-time corrected functional images using SPM's default values. Lastly, all the data was smoothed using a Gaussian kernel of 8 x 8 x 8 mm Full Width at Half Maximum.

A first-level analysis was conducted, with a design matrix specified, reviewed, and estimated for all participants using SPM's default values (including convolution with the canonical Hemodynamic Response Function) to test the different functional task conditions. First-level bidirectional contrasts were created with a design of condition x pre-post time using task onset times derived from the behavioral data in R.

The three contrasts for the Stop Signal were overall inhibition (changes in pre-post activation between the control condition and correct stop trial responses), overall disinhibition (changes in pre-post activation between the control condition and incorrect stop trial responses), and differences between inhibition and disinhibition (changes in pre-post activation between correct and incorrect stop trial responses). Six contrasts were created to examine the activation in these conditions bidirectionally.

The three contrasts for the Stroop were overall conflict monitoring (changes in pre-post activation between the control condition and congruent-incongruent trials), overall conflict resolution (changes in pre-post activation between the control condition and incongruent-incongruent trials), and differences between conflict monitoring and resolution (changes in pre-post activation between incongruent trial types). Six contrasts were created to examine the activation in these conditions bidirectionally.

A second-level analysis was conducted by performing a one sample t-test on the first-level contrasts using default SPM values, with a design matrix specified, reviewed, and estimated

for each contrast. Change in Y-BOCS scores, change in MADRS scores, age, and education were entered in as covariates for the second-level model. Two second-level contrasts looking at general activation and activation correlating with change in Y-BOCS scores were created.

To view significant activations in the regions of interest (ROIs) at the second-level, the WFU-pickatlas (http://fmri.wfubmc.edu/software/PickAtlas) was used to generate ROI masks (Maldjian, Laurienti, Burdette, & Kraft, 2003; Maldjian, Laurienti, & Burdette,2004). For both ROI masks, Brodmann areas, using a 1-point dilation to account for partial volumes, were used. A 1-point dilation on these areas maintains their anatomic location while increasing the region by 1 voxel in each direction (Maldjian, Laurienti, Burdette, & R., 2003; Maldjian, Laurienti, & Burdette, 2004).

For the ROI mask for regions identified as involved in response inhibition, the included areas were as follows: inferior frontal cortex (BA 44, 45, 47), inferior parietal cortex (BA 39, 40), pre-supplementary motor area (BA 6), anterior cingulate cortex (32), anterior insula (BA 13) and subthalamic nucleus (BA subthal nucleus).

For the ROI mask for regions identified as involved in emotion regulation, the included areas were as follows: amygdala (BA amyg), dorsolateral prefrontal cortex (BA 9, 46), anterior cingulate cortex (BA 32), and dorsomedial prefrontal cortex (BA 8, 9, 10, 24, 32). Overlapping areas were accounted for in the mask only once.

These masks were applied to the second-level results and small volume correction was utilized to restrict significant difference testing to those areas of interest, using a voxel threshold set at $p < 0.001$, uncorrected, and a family-wise error (FWE) cluster threshold of $p < 0.05$.

Functional Connectivity Analysis

The first-level preprocessed resting state functional data from SPM was imported into the CONN toolbox, version 21a (Whitfield-Gabrieli & Nieto-Castanon, 2012) running on MATLAB R2019a (MATLAB, 2019). Pre and post conditions were defined in the setup and T1 structural scans were uploaded and underwent CONN's standard structural segmentation and normalization preprocessing pipeline. CONN's default denoising pipeline was used to minimize variability due to physiological and motion effects. This pipeline consists of linear regression of potential confounding effects in the BOLD signal, followed by temporal band-pass filtering. For the linear regression, the pipeline used an anatomical component-based noise correction procedure (aCompCor) to extract noise components from white matter and cerebral spinal fluid components. Participant-motion parameters (imported from SPM preprocessing) and condition effects were also included as covariates in the first-level analyses. For the temporal band-pass filtering, CONN's pipeline removes low-frequency drift and high-frequency noise by applying a band pass filter (0.008-0.9 Hz) on the data (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Seed-to-voxel analyses were conducted on amygdala, frontal orbital cortex, anterior cingulate cortex, and three regions of the default mode network (medial prefrontal cortex, lateral parietal cortex, posterior cingulate cortex). For regions of interest definitions, the CONN toolbox uses cortical and subcortical ROIs defined by the Harvard-Oxford atlas (Makris, et al., 2006; Frazier, et al., 2005; Desikan, et al., 2006; Goldstein, et al., 2007). For regions of interest, amygdala was defined as the average connectivity between the right and left amygdala regions, frontal orbital cortex was defined as the average connectivity between the right and left frontal orbital cortex regions, and the default mode network was defined as the average connectivity between medial prefrontal cortex, left parietal cortex, right parietal cortex, and posterior

cingulate cortex. Anterior cingulate cortex was defined as the connectivity associated with that region (Table 3).

After a first-level analysis was performed on these regions, the same second level covariates used in the activation analyses (delta Y-BOCS, delta MADRS, age, education) were entered and changes in pre-post connectivity was examined in the four regions across all 11 participants. All significant functional connectivity results were set at a voxel threshold of $p < 0.001$, uncorrected, and a one-sided family-wise error (FWE) cluster threshold of $p < 0.025$.

RESULTS

Behavioral Analysis Results

For the emotional Stroop task, there were no significant differences in accuracy between pre-intervention (M = .85, SD = .14) and post-intervention visits (M = .81, SD = .19); t(10) = .84, p = .42. There were also no significant differences in response time between pre-intervention (M = .73, SD = .11) and post-intervention (M = .74, SD = .16); t(10) = -.71, p = 0.49.

For the stop signal task, there were no significant differences in accuracy between pre-intervention (M = .85, SD = .05) and post-intervention (M = .82, SD = .12); t(10) = 1.4, p = .19. There were also no significant differences in response time between pre-intervention (M = .56, SD = .17) and post-intervention (M = .53, SD = .13); t(10) = 1.04, p = .32.

Brain Activation Results

No significant differences in activation between pre-intervention and post-intervention scans were found for any of the contrasts defined for the stop-signal or emotional Stroop functional data. There were no significant correlations between the change in Y-BOCS score and differences in activation for pre-post intervention scans found for any of the contrasts defined for either functional data run.

Resting State Functional Connectivity Results

When examining differences in resting state functional connectivity between pre and post scans, participants showed changes in functional connectivity between the anterior cingulate cortex and the left lateral occipital cortex (peak Montreal Neurological Institute coordinates: x, y, z = -38, -88, -6; cluster size: 147 voxels; cluster-level p_{fwe} = 0.000656).

An analysis was also conducted on pre and post functional connectivity in amygdala; participants showed changes in functional connectivity between amygdala and right lateral

occipital cortex (peak Montreal Neurological Institute coordinates: x, y, z = 42, -64, -22; cluster size: 341 voxels; cluster-level p_{fwe} = 0.000000).

When examining the pre and post functional connectivity in frontal orbital cortex, participants showed changes in functional connectivity between frontal orbital cortex and the general region of right inferior frontal gyrus (peak Montreal Neurological Institute coordinates: x, y, z = 30, 12, 22; cluster size: 114 voxels; cluster-level p_{fwe} = 0.001898), as well as changes in functional connectivity between frontal orbital cortex and the general region of right superior frontal gyrus (peak Montreal Neurological Institute coordinates: x, y, z = 14, 6, 60; cluster size: 87 voxels; cluster-level p_{fwe} = 0.010313). Compared to prior maps, the voxels were more diffuse, with only 52% of voxels for right inferior frontal gyrus appearing in the first cluster and 36% of right superior frontal gyrus appearing in the second identified cluster.

Finally, in examining pre and post functional connectivity in the DMN, participants showed changes in connectivity between the DMN and left inferior temporal gyrus (peak Montreal Neurological Institute coordinates: x, y, z = -46, -46, -16; cluster size: 76 voxels; cluster-level p_{fwe} = 0.023624), and decreased connectivity between the default mode network and right frontal pole (peak Montreal Neurological Institute coordinates: x, y, z = 44, 40, -20; cluster size: 70 voxels; cluster-level p_{fwe} = 0.035312) (Table 4).

DISCUSSION

This study aimed to explore whether one month of intensive ERP treatment altered activation in brain regions associated with EF domains, such as response inhibition and emotion regulation, that have previously been found to display dysfunctional activation in OCD populations. Additionally, this study sought to examine whether improvement in clinically observed improvement in OCD symptoms correlated with differences in brain activation.

Regional Brain Activation

Prior research has established that OCD is associated with behavioral deficits in inhibition and emotion regulation, with corresponding abnormalities in brain regions associated with these domains of function (Menzies, et al., 2008; Stern, Nota, Heimberg, Holaway, & Coles, 2014 de Wit, et al., 2015; Norman, et al., 2019). However, findings from the present study did not find any neurological or behavioral changes for these EF domains after assessing them before and after one month of intensive residential treatment for OCD. Additionally, the current study did not find correlations between changes in OCD symptom severity and brain activation. When examining these findings in consideration of the current literature, it is important to discuss potential explanations for these null results.

Potential explanations for these results differ between the two EF domains. A potential explanation for the lack of changes in inhibitory behavioral outcomes and brain activation in areas associated with inhibition despite treatment exposure and OCD symptom improvement is that this domain of EF may be more accurately conceptualized as a trait, as opposed to a state-dependent, construct in OCD populations. Some studies exploring EF deficits in individuals whose OCD symptoms are in remission have found similar inhibition deficits similar to those whose symptoms are current (Bannon, Gonsalvez, Croft, & Boyce, 2006; Rao, Reddy, Kumar,

Kandavel, & Chandrashekar, 2008; McLaughlin, et al., 2016). This perspective conceptualizes inhibition deficits as endophenotypes of risk factors for the development of OCD, rather than traditional treatment targets. In further support of this hypothesis, additional research has found inhibition deficits in unaffected first-degree relatives of OCD individuals (Menzies, et al., 2007; Zhang, Yang, & Yang, 2015). Overall, these findings challenge the conceptualization of inhibition deficits as a state-dependent trait modifiable by treatment by framing them as a behavioral precursor that may impact the development of obsessive-compulsive symptoms. Thinking of inhibition as a domain of EF that shows persistent impairment regardless of current symptom status would partially explain the present study's null results.

In regard to emotion regulation, the null findings from the present study may be better explained by temporal rather than construct-related theories. The premise for exploring emotion regulation in the current study was the working assumption that an individual engaged in ERP would learn cognitive reappraisal skills that would improve their emotion regulation capabilities. However, while emotion regulation abilities and engagement in beneficial strategies are likely to be beneficial in ERP treatment, there is debate about when those skills are acquired, with some research suggesting that improvements in emotion regulation before, and not during, ERP may lead to better treatment outcomes (Fergus & Bardeen, 2014). Some emotion regulation skill development interventions, such as acceptance and commitment therapy (ACT), have shown benefits for treating OCD, leading researchers to hypothesize that applying emotion regulation interventions prior to ERP engagement may lead to better results (Khosravani, Ardestani, Bastan, & Malayeri, 2020). From this perspective, it may be more informative to examine emotion regulation development in the time leading up to and during ERP engagement to clarify the role of temporal factors for this EF domain.

Another potential explanation for the null behavioral and neuroimaging results may be the impact of OCD severity and the presence of comorbid psychopathology on EF deficits in this clinical population. As noted earlier while discussing general EF findings in OCD, inconsistent results in EF may be due in part to the heterogeneity found in clinical populations, EF operationalization, and the diversity in tests used. Researchers caution against oversimplifying the presentation of EF deficits by presuming that an improvement in OCD symptoms will lead to an equal improvement in EF, especially when other disorders associated with EF deficits are present (Abramovitch & Abramowitz, 2014; Yap, et al., 2018). For cases involving severe clinical OCD, the presence of comorbid psychopathology is common and even individuals who successfully engage with treatment often still have significant clinical symptoms afterwards.

This matter is particularly relevant for the present study, which recruited severe cases of OCD from a residential unit. Even though 6 of 11 participants had a clinically meaningful improvement in symptoms (defined as a 35% decrease in Y-BOCS score), 10 out of 11 participants still met criteria for moderate OCD (defined as a Y-BOCS score 16 or greater) after a month of treatment (Lewin, et al., 2011). None of the 11 participants in the study were at a subclinical threshold (defined as a Y-BOCS score of 7 or less) after one month in the program. This demonstrates an important distinction between clinical improvement and clinical severity when assessing EF deficits in a clinical population. Regardless of overall clinical improvement, it would be expected that individuals demonstrating moderate levels of OCD symptom severity would still experience significant EF deficits and related impairment beyond that of the general population (Abramowitz, 1998). Since nearly all the participants had a notably elevated severity of OCD symptoms even with treatment, it is possible this remaining severity accounts for the lack of changes found in the behavioral and neurological activation results. Given these

considerations, future studies examining the interaction between EF domains and treatment effects in clinical populations should take into consideration how overall clinical severity, temporal factors, and the state-dependency of an EF factor may complicate that interaction.

Functional Connectivity

In addition to examinations of changes in brain activation, the present study conducted an exploratory analysis to determine whether there were significant changes in functional connectivity for regions or networks commonly associated with either OCD or treatment response. Two significant connectivity changes were associated with occipital lobe; one being its connectivity with amygdala and the other indicating changed connectivity with ACC. Given that prior research has indicated visuospatial deficits as part of an OCD neuropsychological profile, change related to a visual processing area of the brain is interesting (Kuelz, Hohagen, & Voderholzer, 2004; Rao, Reddy, Kumar, Kandavel, & Chandrashekar, 2008). Recent connectivity research has also implicated occipital lobes as being more functionally relevant in OCD than previously thought given its connectivity to areas of the salience network, like ACC, during symptom provocation tasks (Ravindran, et al., 2020). Additionally, prior research has identified connectivity between amygdala and occipital lobe regions of the brain while processing emotional information, with alterations in this connectivity being observed in participants with OCD who responded to cognitive-behavioral therapy (Gao, et al., 2021). Thus, while the current findings are more descriptive and exploratory in nature, finding a change between a visual processing region and two regions involved with attention and emotion processing is supported by the current connectivity literature.

Involvement of orbitofrontal cortex in emotion and reward has made it a key figure in many theoretical models of OCD, which highlight orbitofrontal dysfunction as a key impairment

of the disorder, and this distinction has been supported by early neuroimaging work with OCD (Menzies, et al., 2008). Prior research has linked the orbitofrontal cortex and areas of the frontal gyrus, particularly the inferior frontal gyrus, to reward circuits (Du, et al., 2020), with research indicating dysfunctional connectivity in this area for depression (Rolls, et al., 2020). Areas of frontal gyrus and orbitofrontal cortex work together to process rewards and punishment in the brain, linking these areas additionally to emotion processing. Despite strong evidence for its role in OCD, research examining connectivity with orbitofrontal cortex has produced inconsistent findings (Liu, et al., 2022). Given the established involvement of these regions with diagnoses such as depression, the comorbidity found in clinical OCD populations also poses a challenge in result interpretation. Preliminary findings found in the present study showing alterations between orbitofrontal cortex and regions of frontal gyrus potentially indicate changes in connectivity within this reward circuitry. Given the importance of orbitofrontal cortex in theoretical conceptualizations of OCD, clarifying prior inconsistent findings in this area presents an important direction for future research.

The DMN is a network associated with internalizing processes, but has shown unique activation patterns in OCD due to stronger interconnectivity between it and regions associated with processing external stimuli (Beucke, et al., 2014). The differences observed in this network have been hypothesized to occur due to the internalizing symptoms of OCD (obsessions) often focusing on external occurrences (Beucke, et al., 2014). In examining DMN connectivity pre- and post- treatment, two smaller clusters of altered connectivity were identified in the present study; one with inferior temporal gyrus and one within frontal pole. These preliminary findings are difficult to interpret given the currently available research literature. While other areas of temporal cortex have been implicated in memory and have demonstrated connectivity with the

DMN, inferior temporal gyrus is not part of those findings (Beucke, et al., 2014). Therefore, while altered connectivity patterns in the DMN have been identified in OCD, the lack of prior research indicating a role of inferior temporal gyrus in those patterns makes interpretation difficult (Ravindran, et al., 2020). Another DMN connectivity cluster showing significant changes in connectivity was identified by the CONN toolbox atlas to occur in the 'right frontal pole,' with 63% of the cluster (29 voxels) occurring in that region. The frontal lobe is associated with internally and externally focused cognition, but the small number of voxels and lack of anatomical specificity for this cluster makes interpreting these findings difficult (Moayedi, Salomons, Dunlop, Downar, & Davis, 2015). Overall, connectivity findings from the present study indicate changes between the DMN and other regions of frontal cortex involved in higher order cognitions, though smaller cluster sizes and limited prior research makes nuanced interpretations difficult.

Limitations

This study has several limitations. A primary limitation is the very small sample size of 11 participants, which may have led to an underpowered analysis unable to accurately capture subtler effects. This sample was also demographically homogenous with regards to race, socioeconomic status, education, and age, potentially compromising the external validity of these findings. Additionally, it would have been beneficial to have a healthy control population to provide baselines for EF performance and neurological profiles.

Additionally, participants were on different and changing medication regimens and presented with different comorbid diagnoses, making the sample very clinically heterogenous. While there were mixed indications in the literature about how comorbid diagnoses and medication may affect EF and neuroimaging outcomes, ideally these factors would be better

controlled for as much as possible given this population (Morein-Zamir, Fineberg, Robbins, & Sahakian, 2010).

Multiple papers in the field have discussed the heterogeneity of OCD itself with regards to symptom dimension, with some addressing how different symptom presentations may affect other aspects of clinical presentation (like EF deficits) and treatment response (Abramovitch & Abramowitz, 2014; Berman, Shaw, & Wilhelm, 2018). In the current study, participants with predominantly germ and contamination symptoms were overrepresented compared to other potential dimensions, which may have affected the outcomes found.

Apart from population statistics, some aspects of study design could have been changed to strengthen some of the findings. Emotion regulation was measured using an emotional Stroop task, which is an established task for that purpose. However, it would have been beneficial to include either scales assessing emotion regulation directly or to use a task that more purely operationalizes emotion regulation, given that Stroop-like tasks have an additional inhibition component due to their design.

Conclusion

Despite limitations and null findings, the behavioral and brain activation results from this study provide more information about the relationship between executive functions, treatment outcomes, and neuroimaging markers in this clinical population. Additionally, the exploratory functional connectivity findings provide preliminary evidence that could guide future research directions.

TABLES

Table 1: Demographic Characteristics

	OCD n = 11	
Characteristic	Pre-ERP	Post-ERP
Age, yr	24.1 ± 5.2	
Female/male, n	7/4	
Education, yr	14.8 ± 2.4	
Illness duration, yr	11.6 ± 6	
Y-BOCS score	28.9 ± 3.6	20.3 ± 4.8
△ Y-BOCS score	8.6 ± 4	
MADRS score	13.5 ± 7.1	8.3 ± 5.4
△ MADRS score		
Primary OCD Dimension^:		
Germs and Contamination	6	
Responsible for Harm, Injury, or Bad Luck	2	
Unacceptable Thoughts	2	
Symmetry, Completeness, or "Just Right"	1	
^Determined by averaging DOCS scores across visits		

Table 2: Extended Demographics (Comorbid Diagnoses and Medication)

Current Comorbid Diagnoses*:	None	2
	Major Depressive Disorder	3
	PTSD	3
	Social Phobia	3
	ADHD	1
	Agoraphobia	1
	Body Dysmorphic Disorder	1
	Bulimia	1
	Dysthymic Disorder	1
	Generalized Anxiety Disorder	1
	Specific Phobia	1
Past Comorbid Diagnoses:	ADHD	2
	Alcohol Dependence	1
	Major Depressive Disorder	1
	Generalized Anxiety Disorder	1
Psychotropic Medications":	Abilify	2
	Buspar	1
	Clomipramine	3
	Clonazepam	2
	Gabapentin	1
	Lexapro	2
	Lithium	1
	Lorazepam	1
	Luvox	1
	Namenda	1
	Paxil	1
	Phanelzine	1
	Prozac	3
	Risperidone	1
	Seroquel	2
	Viibryd	1
	Zoloft	2
	Zyprexa	1

*1 participant missing SCID data

" Due to ongoing medication changes, this list includes the number of participants who were on this medication for at least one study visit

PTSD = Post-Traumatic Stress Disorder; ADHD = Attention-Deficit Hyperactivity Disorder

Table 3: Resting State ROI Labels

Region	Labels in CONN Toolbox
ACC	Salience.ACC (0, 22, 35)
Amygdala (averaged)	
Amygdala (left)	atlas.Amygdala r
Amygdala (right)	atlas.Amygdala l
Frontal Orbital Cortex (averaged)	
Frontal Orbital Cortex (left)	atlas.Forb l (Frontal Orbital Cortex Left)
Frontal Orbital Cortex (right)	atlas.Forb r (Frontal Orbital Cortex Right)
Default Mode Network (averaged)	
Medial Prefrontal Cortex	networks.DefaultMode.MPFC (1, 55, -3)
Lateral Parietal Cortex (left)	networks.DefaultMode.LP(L) (-39, 077, 33)
Lateral Parietal Cortex (right)	networks.DefaultMode.LP(R) (47, -67, 29)
Posterior Cingulate Cortex	networks.DefaultMode.PCC (1, -61, 38)

Table 4: Resting State Seed-Based Connectivity Map Results

Region	Peak coordinates (MNI mm) x	y	z	Cluster size (voxel)	Approximate Brain Region
ACC	-38	-88	-6	147	Left Lateral Occipital Cortex
Amygdala (averaged) Amygdala (left) Amygdala (right)	42	-64	-22	341	Right Lateral Occipital Cortex
Frontal Orbital Cortex (averaged)	30	12	22	114	Right Inferior Frontal Gyrus
Frontal Orbital Cortex (left) Frontal Orbital Cortex (right)	14	6	60	87	Right Superior Frontal Gyrus
Default Mode Network (averaged) Medial Prefrontal Cortex	-46	-46	-16	76	Left Inferior Temporal Gyrus
Lateral Parietal Cortex (left) Lateral Parietal Cortex (right) Posterior Cingulate Cortex	44	40	-20	70	Right Frontal Pole
Defined using the Harvard-Oxford atlas.					

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