Cognitive sequences in obsessive-compulsive disorder are supported by frontal cortex ramping activity and mediated by symptom severity

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Author Contributions

Hannah Doyle: Data Curation, Conceptualization, Investigation, Methodology, Formal Analysis, Writing – Original Draft, Writing – Reviewing and Editing, Visualization. Sarah Garnaat: Conceptualization, Methodology, Investigation & Training in Clinical Assessments, Clinical Resources, Writing – Reviewing and Editing, Supervision of Clinical Activities, and Funding Acquisition. Nicole McLaughlin: Conceptualization, Methodology, Investigation & Training in Clinical Assessments, Clinical Resources, Writing – Reviewing and Editing, Supervision of Clinical Activities, and Funding Acquisition. Theresa M. Desrochers: Conceptualization, Methodology, Software, Validation, Writing – Original Draft, Writing – Reviewing and Editing, Supervision, Funding Acquisition.

Abstract

Completing sequences is a part of everyday life. Many such sequences can be considered abstract – that is, defined by a rule that governs the order but not the identity of individual steps (e.g., getting dressed for work). Over-engagement in ritualistic and repetitive behaviors seen in obsessive-compulsive disorder (OCD) suggests that abstract sequences may be disrupted in this disorder. Previous work has shown the necessity of the rostrolateral prefrontal cortex (RLPFC) for abstract sequence processing and that neural activity increases (ramps) in this region across sequences (Desrochers, Chatham, & Badre, 2015; Desrochers, Collins, & Badre, 2019). Neurobiological models of the cortico-striatal-thalamo-cortical (CSTC) loops describe prefrontal circuitry connected to RLPFC and that is believed to be dysfunctional in OCD. As a potential extension of these models, we hypothesized that neural dynamics of RLPFC could be disrupted in OCD during abstract sequence engagement. We found that neural dynamics in RLPFC did not differ between OCD and healthy controls (HCs), but that increased ramping in pregenual anterior cingulate cortex (pACC), and superior frontal sulcus (SFS) dissociates these two groups in an abstract sequence paradigm. Further, we found that anxiety and depression symptoms mediated the relationship between observed neural activity and behavioral differences observed in the task. This study highlights the importance of investigating ramping as a relevant neural dynamic during sequences and suggests expansion of current neurobiological models to include regions that support sequential behavior in OCD. Further, our results may point to novel regions to consider for neuromodulatory treatments of OCD in the future.

Introduction

Sequences define the way humans organize their lives, often imposing a scaffold we can use to help achieve our goals. Many such sequences can be considered abstract, in that they are defined by a rule governing a series of operations rather than by the identity of the operations themselves (Desrochers et al., 2022). For example, one uses the structure of a recipe to guide the sequence of cooking pasta (e.g., boil water for noodles, chop the vegetables, grate the cheese), with the flexibility of using tomatoes from the garden or the store without disrupting the process. In daily life, these abstract sequences appear disrupted in obsessive-compulsive disorder (OCD), which is characterized by obsessions and associated compulsive behaviors. Common repetitive behaviors or rituals in those with OCD, such as counting in groupings of a certain number (e.g. 5) (Menon, 2013), repeatedly going in and out of a doorway, or dressing and re-redressing in the morning (Uvais & Sreeraj, 2016) can be conceptualized as dysfunctional engagement in abstract sequences. While neural correlates of abstract sequential control are increasingly understood in healthy populations, the underlying neural mechanism of abstract sequential behavior in OCD, however, remains unknown.

Observed behavioral manifestations along with previous work suggest that abnormal neural circuitry may underly abstract sequential behavior deficits in OCD. Previous work in abstract sequences has established strong behavioral and neural markers of sequential control. Behaviorally, healthy controls exhibit significantly increased reaction times at sequence onset compared to later sequence positions (Desrochers et al., 2015, 2019; Schneider & Logan, 2006). Neurally, activity increases (ramps) during abstract sequences, and the rostrolateral prefrontal cortex (RLPFC) is necessary for their completion (Desrochers et al., 2015, 2019). Given this, we hypothesized RLPFC dysfunction may underlie deficits in abstract sequential behavior in OCD. Taken together, this evidence suggests that disruption in this specific circuitry may underlie disrupted behavioral patterns in everyday life, manifesting in commonly observed clinical symptoms.

Neurobiological models support hypotheses of disrupted RLPFC activity and ramping during abstract sequential behavior in OCD. One theory of OCD dysfunction specifically implicates PFC deficits in the memory of behavioral sequences termed "structured event complexes," which have beginnings and ends and are inherently rewarding (Huey et al., 2008). Further, biological models have implicated the cortico-striatal-thalamo-cortical (CSTC) loops as dysfunctional in OCD during various cognitive processes (Milad & Rauch, 2012; Shephard et al., 2021). Although RLPFC is not directly stated in these models, it is interconnected to dorsolateral PFC in the dorsal cognitive circuit and the ventrolateral PFC in the ventral cognitive circuit, both of which are found to be dysfunctional in OCD during cognitive control and affective paradigms (Shephard et al., 2021). Furthermore, these prefrontal cortical regions have been shown to be underrecruited in OCD during task switching and set-shifting tasks (Gu et al., 2008; Meiran, Diamond, Toder, & Nemets, 2011), which similarly to sequential control require flexible goal maintenance to complete. As ramping occurs during other cognitive processes shown to be dysfunctional in OCD, such as error monitoring (Meek, Fotros, Abo Aoun, & Modirrousta, 2021; A. Riesel, Klawohn, Kathmann, & Endrass, 2017; Anja Riesel, Kathmann, & Klawohn, 2019) and reward processing (Figee et al., 2011; McKim & Desrochers, 2022), in regions of the CSTC (Norman et al., 2019), ramping as a dynamic in RLPFC may further implicate this region in the pathology of the disorder.

Symptom severity may also play a role in success in carrying out abstract sequences in OCD. In cognitive control tasks that require task switching, OCD symptom severity (total Yale-Brown Obsessive Compulsive Scale or Y-BOCS scores) have been found to correlate with task deficits, including delayed reaction times and attentional deficits (Okutucu, Kırpınar, Deveci, & Kızıltunç, 2023). Depression and anxiety, highly comorbid with OCD, have also been found to correlate with performance deficits in set-shifting (Snyder, 2013) and cognitive inhibition (König, Steber, Borowski, Bliem, & Rossi, 2021). Other work has shown that depression correlates with activity in the superior frontal sulcus (Dotson et al., 2014)and depression and anxiety correlate with lateral PFC activity (Yeung, Lee, & Chan, 2021) during working memory tasks. OCD, depression, and anxiety may therefore also correlate with RLPFC neural dynamics during abstract sequence behavior. The relationship between neural activity and cognitive control task performance may relate to overall OCD symptomatology.

Using functional magnetic resonance imaging (fMRI), we investigated abstract sequential behavior and its neural underpinnings in participants with OCD and healthy controls. We observed error rate deficits in OCD, overall, in the task. RLPFC neural dynamics did not differ between groups, but increased ramping activity in pregenual anterior cingulate cortex (pACC) and superior frontal sulcus (SFS) occurred in OCD vs. HC to support abstract sequence behavior. Additionally, anxiety and depression were found to mediate the relationship between neural activity and behavioral differences observed in OCD. Our results inform current neurobiological models of OCD.

Methods

Participants

Participants were recruited via online advertising, fliers, and word of mouth. All participants gave informed, written consent as approved by the Butler Hospital Institutional Review Board. Initially, 76 participants were recruited. Of these, 16 dropped out or were screened out of the study and therefore did not advance to the fMRI scan, resulting in 60 scanned in total. Two participants were excluded for excessive motion, one due to user error in handling the button box, seven due to poor behavioral performance (overall error rates > 20%). As previous studies using this task have demonstrated, error rates below 20% ensured participants were completing the task as instructed (Desrochers et al., 2015, 2019; Schneider & Logan, 2006; Trach, McKim, & Desrochers, 2021). After excluding participants, our final sample size was 50 in total, 25 in the HC group (mean 28.9 yrs (+/- 10.7 [SD]); 11 m [14 f]), and 25 in the OCD group (mean 25.8 yrs (+/- 8.5 [SD]); 3 m [22 f]). The original target sample size was 26 in each group based on a power analysis used to determine sample size in a previous study using this paradigm in healthy controls (Desrochers et al., 2015), however, a post-hoc power analysis determined we achieved 78% power given a sample size of 25 in each group for an effect size of 0.5 (Cohen's d).

Inclusion criteria for the healthy control group were as follows: 18 - 55 years of age, right-handed, ability to communicate in English to perform study procedures and provide consent. OCD group inclusion criteria followed that of the healthy control group with the following additions: current DSM-5 diagnosis of OCD and Y-BOCS score of equal to or greater than 16, no use or stable psychiatric medication use for 6 weeks prior to study enrollment,

limited to serotonin reuptake inhibitors and PRN use of benzodiazepines. Healthy control group exclusion criteria were as follows: current psychiatric diagnosis, lifetime diagnosis of psychotic disorder, bipolar mood disorder or OCD, active suicidal ideation, significant neurological pathology, use of psychiatric medications, contraindications to MRI scan (e.g., ferromettalic implants, pregnancy, or other conditions that pose safety risk). OCD exclusion criteria were as follows: active problematic substance use, lifetime diagnosis of psychotic or delusional disorder, clinically significant hoarding symptoms, active suicidal ideation, significant neurological pathology, and contraindication to MRI scans.

Each participant completed an interview and an in-person fMRI. The clinical interview visit consisted of completing informed consent, and administration of clinical interviews and self-report measures (as described below). Participants could only proceed to the fMRI portion if they were still eligible for the experiment after the clinical interview. The second session was an fMRI scan conducted at the Brown University MRI Research Facility. To overview the scan session, participants were first trained on the task and then completed 5 runs of the task in the MRI scanner. Participants were compensated $25 for the first session and $75 for the second. Participants who were ineligible for the fMRI portion were only compensated for the clinical interview visit.

Measures

The cognitive task and clinical interviews were administered by trained evaluators (see description of, below), and participants completed additional self-report measures.

<u>*Clinician Administered:*</u>

Structured Clinical Interview for DSM-5 (SCID-5) (Brown & Barlow, 2014) is an evaluator-administered semi-structured interview to assess for presence or absence of specific psychiatric disorders. In this study, selected modules of the SCID-5 were used to assess the following modules: mood disorders, anxiety disorders, OCD and related disorders, and trauma-related disorders. Additional SCID-5 modules were used to screen for psychotic disorders and hoarding disorder, which were excluded in the present study.

Yale-Brown Obsessive-compulsive Scale (Y-BOCS) (Goodman et al., 1989): The Y-BOCS symptom checklist is an evaluator administered measure used to assess presence or absence of common OCD symptoms. The accompanying Y-BOCS severity scale is an evaluator-administered assessment of OCD symptoms severity measured over the past week. The Y-BOCS is considered the gold-standard measure of OCD symptom severity.

<u>*Self-report:*</u>

Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993): The AUDIT is a 10-item self-report questionnaire that assesses alcohol consumption, drinking behaviors, and alcohol-related problems. A score of 8 or above was used as a cut-off for men, while a score of 6 or above was used as exclusion criteria for women. Scores range from 0 - 40, with a higher score indicating more alcohol use.

Drug Use Disorders Identification Test (DUDIT) (Berman, Bergman, Palmstierna, & Schlyter, 2016): The DUDIT is an 11-item self-report measure that assesses current drug-related problems or drug abuse. A score of 6 or higher was used as an exclusion criterion for men while a score of 2 or higher screened out women in the current study. Scores range from 0 - 44, with higher scores indicating more drug use.

Quick inventory of depressive symptomatology (QIDS-SC) (Rush et al., 2003): The QIDS-SC is a 16-item self-report measure of depression severity. Scores range from 0 - 27, with higher scores indicating more severe symptoms.

Depression, anxiety, and stress scale (DASS-21) (Osman et al., 2012): The DASS is a 21-item (shortened from the original 42-item) questionnaire that measures the related emotional states of depression, anxiety, and stress. Scores range from 0 - 42, with higher scores reflecting more severe negative emotional states.

Overall anxiety severity and impairment scale (OASIS) (Campbell-Sills et al., 2009): The OASIS is a 5-item trans-diagnostic measure that can be used to assess the severity and impairment of one or more anxiety disorders. Scores range from 0 - 20, with higher scores indicating more severe anxiety symptoms.

Task Design and Procedure

Overview

The abstract sequence task used in this study was used in a previous study in healthy controls (**Figure 1**) (Desrochers et al., 2015) and was based on previous studies of sequential control (Schneider & Logan, 2006). Participants were presented on each trial with a stimulus of varying size (small [3.5 x 3.5 cm] or large [7 x 7 cm]), shape (circle or square), and color (red or blue), for a total of 8 possible stimuli that appeared equally throughout the task and did not repeat on adjacent trials. After each trial was an intertrial interval, displayed as a white fixation cross centered on a black screen, with jittered timing (0.25 - 8 s). Participants were provided 4 seconds on each trial to make a response. Each trial had response options for the color and shape of the stimulus, mapped onto two response pad buttons, corresponding to the index and middle finger of the right hand. Each response option was one shape and color combination (e.g., index finger button maps onto both 'blue' and 'circle' and the middle finger maps onto 'red' and 'square'). Participants pressed one button per trial to indicate their response. Response options were always shown on the bottom left and right of the screen. Stimulus-response mappings were kept consistent throughout the experiment but were counterbalanced across participants. The frequency of responses to each stimulus and the response repeats (instances when the same finger was used to respond to two trials in a row) were counterbalanced throughout the task.

Stimuli were presented in blocks (24-27 trials, so that blocks ended on unpredictable sequence positions, counterbalanced across blocks), and participants completed 4 blocks per run, 5 runs total. At the beginning of each block, participants were shown a 4-item sequence (5 s), which they used to make a choice on every trial, followed by a fixation screen (1 s). Every block consisted of a sequence that was one of two types: simple (of the pattern AABB; specifically "COLOR COLOR SHAPE SHAPE" or "SHAPE SHAPE COLOR COLOR") or complex (of the

pattern ABBA; specifically "COLOR SHAPE SHAPE COLOR" or "SHAPE COLOR COLOR SHAPE"). Simple sequences contained one embedded task switch (e.g., switching on positions 2 to 3 from "COLOR" to "SHAPE" in the sequence "COLOR COLOR SHAPE SHAPE") while complex sequences contained two embedded task switches (e.g., switching on positions 1 to 2 from "COLOR" to "SHAPE" in the sequence "COLOR SHAPE SHAPE COLOR"). The number of task switches was equivalent across blocks, so that the probability of occurring switch or repeat trials was equal between blocks of complex and simple sequences. At the end of each block, participants were shown a screen that asked what sequence position they would be on if they were to make a choice on the next trial. Participants responded to this question using one of four buttons on the response pad (excluding the thumb button). The order of simple and complex sequence blocks were counterbalanced across runs.

Participants were trained on an Alienware M17xR4 laptop (Windows 10) using a five-button response pad on four shortened task blocks prior to scanning. Participants completed practice on response pad buttons and then were guided by the experimenter on each trial for the first practice block. Participants performed the remaining practice blocks independently. Performance competency was established by error rates less than 20% overall on the practice sequences (Desrochers et al., 2015, 2019; Schneider & Logan, 2006; Trach et al., 2021). Once this behavioral threshold was reached, participants were scanned while performing the task. The same equipment was used for training as for displaying the task and making responses during scanning. Stimuli were projected onto a 24" BOLDscreen 32 UHD and the task was run using Psychtoolbox on Matlab 2017b.

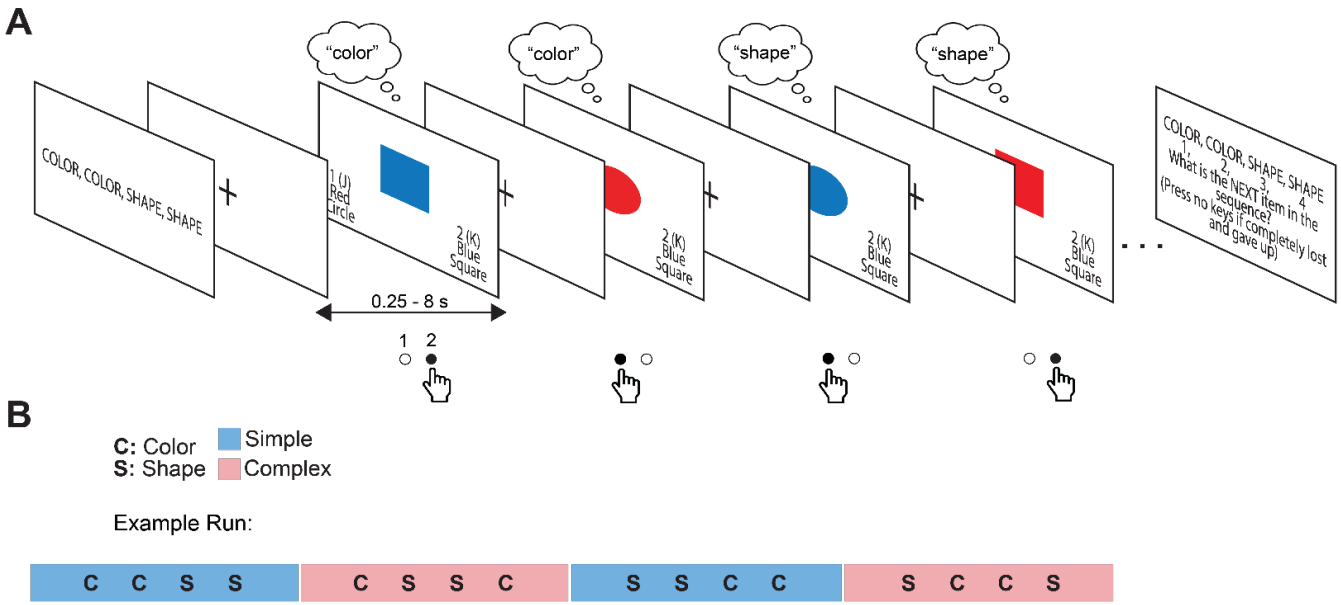

Figure 1. **Abstract sequence task schematic. A.** Example trials in a block for the simple sequence. Each block begins with a screen that instructs the sequence, e.g., "COLOR, COLOR, SHAPE, SHAPE". Each trial consists of one stimulus presentation where the participant must make the correct categorization decision based on the identity of the stimulus and the position in the sequence. The remembered categorization decision for each item is indicated in a thought bubble and the correct choices for each trial are indicated by black arrows. The stimulus remains on screen until a response is made (max 4 sec). After the response (or response time-out), a fixation cross is displayed for the duration of the intertrial interval (ITI, jittered 25 - 8000 ms). Distance between images is for illustration purposes only and does not represent actual timing. There are 24-27 trials per block, it can end on any position in

the sequence, and the block ends with a sequence position question asking, "What is the NEXT item in the sequence?". **B.** Example run containing four blocks, with each block being a simple (CCSS [color, color, shape, shape]; SSCC [shape, shape, color, color]) or complex (CSSC [color, shape, shape, color]; SCCS [shape, color, color, shape]) sequence. The order of the blocks is counterbalanced across the five runs that each participant performs.

Data Acquisition

A Siemens 3T PRISMA MRI scanner with a 64-channel head coil was used for whole-brain imaging. Functional data for two of the 50 participants were acquired using an echo-planar imaging pulse sequence (repetition time, TR = 2.0 s; echo time, TE = 28 ms; flip angle 90°; 38 interleaved axial slices; 3.0 x 3.0 x 3.0 mm). Anatomical scans included a T1-MPRAGE (TR, 1900 ms; TE, 3.02 ms; flip angle, 9.0°; 160 sagittal slices; 1.0 x 1.0 x 1.0 mm) and a T1 in- plane scan (TR, 350 ms; TE 2.5 ms; flip angle, 70°; 38 transversal slices; 1.5 x 1.5 x 3.0 mm). The remaining 48 participants were scanned on an updated protocol designed to enhance signal to noise ratio of the data. Functional data for these participants were acquired using an echo-planar imaging pulse sequence (repetition time, TR = 1.53 s; echo time, TE = 33 ms; flip angle 62°; 60 interleaved axial slices; 2.4 x 2.4 x 2.4 mm). Anatomical scans included a T1-MPRAGE and a T1 in- plane scan with the same parameters as in the original protocol.

Data Analysis

Preprocessing

All imaging data were preprocessed using Statistical Parametric Mapping (SPM12) in Matlab 2017b. Participants with motion exceeding one voxel (3.0 mm for the first two participants and 2.4 mm for the remaining 48 participants) were excluded from analysis. Images were then resampled to account for differences in acquisition timing and matched to the first slice. All images were then corrected for motion using B-spline interpolation and normalized to the Montreal Neurological Institute (MNI) stereotaxic template with affine regularization. Lastly, data were smoothed using an 8mm full-width at half-maximum Gaussian kernel, and resampled using trilinear interpolation.

FMRI Models

All general linear models were constructed using SPM12 and custom scripts in Matlab 2023a. Onset and parametric regressors were convolved with the canonical hemodynamic response function (HRF). Additionally, onset regressors were convolved with the first time derivative of the HRF. Nuisance regressors were included to account for variance due to translational and rotational motion (x, y, z, roll, pitch, yaw) and for the first four trials (first sequence) of every block, time during instruction, and sequence position question trials.

Beta values related to regressors were estimated using a subject-specific fixed-effects model. Whole brain contrasts estimated subject-specific effects, and these estimates were entered into a second-level analysis with subject treated as a random effect. T-values resulting from these contrasts were used for analyses. Whole brain group voxel-wise effects were corrected for multiple comparisons using extent thresholds at the cluster level to yield family-wise error correction and were considered significant at $P < 0.05$. Group level contrasts were rendered on a

3D brain using Connectome Workbench (humanconnectome.org/software/connectome-workbench).

Onsets models: We constructed stimulus onset regressors to model univariate effects at each sequence position. These regressors were modeled as 0 second durations at the onset of each stimulus Separate regressors were included for each position in the sequence (1-4) and each sequence type (complex and simple), for a total of eight regressors for the conditions of interest.

Parametric ramp model: To test for ramping activity, we constructed a regressor for each sequence type (complex and simple) that included a zero-duration onset for each stimulus and a parametric (numbers 1-4) for a linear increase across the four positions in the sequence. Onsets and parametric regressors were estimated hierarchically, such that variance assigned to the parametric regressor was above and beyond what could be accounted for by the stimulus onset alone.

ROI Analysis

Region of interest (ROI) analyses complemented whole-brain analyses. ROIs for replication analyses were taken from a previous study (Desrochers et al., 2015). ROIs were defined from significant peaks of activation from the Onsets model voxelwise contrasts No Position 1 Switch > Repeat; Position 2,3 Switch > Position 2,3 Repeat, and from the Parametric model contrast Parametric Ramp > Baseline. We extracted T values from these ROIs using these contrasts. Repeated measures analysis of variance (RM-ANOVAs) or t-tests were subsequently performed on these values.

Behavior

All behavior analyses were conducted using custom scripts in Matlab 2023a. As in previous studies using the same or similar sequential tasks (Desrochers et al., 2015, 2019; Schneider & Logan, 2006; Trach et al., 2021), the following sets of trials were excluded from remaining analyses. The first four trials (first sequence) in every block were removed across participants (approximately 1.6% of trials per participant) to prevent changes in reaction times (RTs) at block initiation from confounding with RT changes due to sequence initiation or task switching. Additionally, trials were excluded that had RTs < 100 ms (< 1 % of trials per participant) to prevent inclusion of trials in which categorization choices were guessed. Error rates (ERs) were calculated on the remaining trials. Periods of trials were also removed in which participants "lost track" of the sequence. These trials were defined as "lost" for 2 or more error trials up until the next 4 correct adjacent trials occurred (approximately 6.4% of trials per participant). "Lost" trials were excluded to ensure all analyzed trials were ones in which the participants were completing the task as instructed. Statistical analyses were conducted on RTs and ERs using RM-ANOVAs and t-tests.

Age was included as a covariate in all ANOVAs due to a larger age range in the present sample (18-55) compared to previous sequence studies (18-35) (Desrochers et al., 2015; Trach et al., 2021) and to account for the potential impact age has on cognitive task performance (Artuso, Cavallini, Bottiroli, & Palladino, 2017). Sequence initiation cost was calculated as the difference in position 1 and position 3 RTs across sequence types. This calculation averaged RTs across all trials for each participant by positions 1 and 3. These averaged RTs were subsequently subtracted, resulting in one initiation cost number per participant. Sequence costs were calculated

as the RT and ER difference between complex and simple sequences. In these calculations, RTs and ERs were averaged across all trials for each participant by each sequence type (i.e., one average across positions 1-4 complex and one across positions 1-4 simple), and subsequently subtracted to return one sequence cost number per participant. Switch costs were defined as the RT and ER differences between switch and repeat trials. Switch costs were calculated by averaging RTs and ERs across all trials that are switches, which excluded position 1 and included positions 2 and 4 in complex sequences and position 3 in simple sequences and subtracting averaged RTs and ERs across all repeat trials, which excluded position 1 and included position 3 in complex and positions 2 and 4 in simple sequences. This calculation results in an average switch cost number per participant.

Clinical symptom measures (OASIS, DASS anxiety subscale, DASS depression subscale, Y-BOCS) were correlated (pairwise linear) with behavior costs and neural activity in OCD. Mediation analyses were defined as a step-wise series of three linear models: neural activity ~ behavior (direct effect), neural activity ~ clinical measure score (indirect effect), and behavior ~ neural activity + clinical measure score (total effect). The results of the first linear model were required to be significant ($P < 0.05$) to execute the second linear model, which had to yield significance to perform the third model. Partial mediation was defined as lessening of the estimate of the direct effect when the clinical measure scores were incorporated in the third model. Full mediation was defined as the loss of significance of the direct effect after the clinical measure scores were incorporated in the third model.

Results

OCD participants exhibit sequential error rate deficits

To address questions of potential behavioral and neural deficits in abstract sequential processing in OCD, two groups of participants (OCD and healthy control, HC) completed abstract cognitive task sequences (**Figure 1**) while undergoing fMRI scanning. Briefly, participants were presented at each block start with four-item sequences of simple categorization decisions, either simple (containing one task switch, e.g. shape, shape, color, color) or complex (containing two task switches, e.g., shape, color, color, shape). On each trial, participants used information about sequence position to correctly categorize the color or shape of the image. Participants repeated sequences until the end of each block. To probe neural mechanisms underlying sequential behavior, participants completed five runs, each containing four blocks of this task while undergoing fMRI scanning. Three features of this task are relevant to assessing performance: two sequential control features (initiation and sequence cost) and one more general cognitive control feature (switch cost) (Desrochers et al., 2015; Schneider & Logan, 2006). Initiation cost is the difference in RTs between sequence positions 1 and 3 (both positions are repeats or switches, to account for trial type effects), while sequence cost is the RT and ER difference in complex and simple sequences. Switch cost (Monsell, 2003) is the RT and ER difference between switch and repeat trials, excluding the first position.

Participants in both HC and OCD groups replicated sequential and cognitive control effects observed previously. Overall, participants in both groups completed the task as instructed and performed well (HC RTs: 1.23 s (mean) +/- 0.29 s [1 SD], ERs: 7.78 (mean) +/- 7.33 [1 SD]; OCD RTs: 1.32 s (mean) +/- 0.29 s [1 SD], ERs: 8.52 (mean) +/- 7.04 [1 SD]). Both groups

separately exhibited RT effects observed previously: initiation costs (HC: 0.15 s (mean) +/- 0.09 s [1SD]; OCD: 0.18 s (mean) +/- 0.13 s [1 SD]), sequence costs (HC: 0.07 (mean) +/- 0.08 [1 SD]; OCD: 0.06 (mean) +/- 0.11 [1 SD]), and switch costs (HC: 0.13 (mean) +/- 0.12 [1 SD]; OCD: 0.11 (mean) +/- 0.08 [1 SD]). Participants in both groups therefore replicated significant behavior effects observed in previous studies both in sequential (initiation and sequence costs) and general cognitive (switch costs) control.

We tested the hypothesis that OCD participants would exhibit sequential behavior differences compared to HCs. We tested three measures, initiation, sequence, and switch costs, in RTs and ERs between groups. There were no significant differences in RT initiation cost between OCD and HC groups (**Figure 2A**; **Table 1**). RTs were specifically investigated to examine initiation costs as this effect has been observed in RTs previously in sequential tasks (Desrochers et al., 2015; 2019; Trach et al., 2021). Sequence costs showed no significant RT group differences (**Figure 2A**; **Table 1**) but in ER sequence costs were marginally smaller in OCD than in HC, producing an interaction (**Figure 2B, C; Table 1**). Similarly, RT switch costs were not different between groups (**Figure 2A**; **Table 1**) but in ER there were smaller switch costs in OCD compared to HCs (**Figure 2B, D**; **Table 1**). In support of our hypothesis, these ER results suggest that both sequential and general cognitive control was impaired in OCD.

Reaction Times (RTs)	*dfs*	*F*	*p*	*ηp2*	**Error Rates (ERs)**			
Initiation Costs								
Group	1,47	0.7	0.4	0.02	1,47	0.1	0.72	0
Age	1,47	1.2	0.27	0.03	1,47	0.4	0.52	0.01
Position	1,47	8.2	0.01	0.15	1,47	0.2	0.7	0
Group x Position	1,47	1	0.32	0.02	1,47	3.4	0.07	0.07
Age x Position	1,47	0.1	0.71	0	1,47	0.3	0.6	0.01
Sequence Costs								
Group	1,47	0.7	0.42	0.01	1,47	0.1	0.8	0
Age	1,47	1.4	0.24	0.03	1,47	0.4	0.55	0.01
Sequence type	1,47	3.1	0.08	0.06	1,47	1.7	0.2	0.03
Group x Sequence type	1,47	0.4	0.55	0.01	1,47	3.2	0.08	0.06
Age x Sequence type	1,47	0.1	0.82	0	1,47	0.2	0.7	0
Switch Costs								
Group	1,47	0.6	0.46	0.01	1,47	0	0.9	0
Age	1,47	1.6	0.22	0.03	1,47	0.3	0.58	0.01
Trial type	1,47	11.7	0	0.2	1,47	6.4	0.01	0.12
Group x Trial type	1,47	0.8	0.38	0.02	1,47	7.6	0.01	0.14

Age x Trial type	1,47	0.8	0.37	0.02	1,47	0.7	0.4	0.01

Table 1. rmANOVAs of RT (s) and ER (%) initiation costs, sequence and switch costs between OCD and HC groups. Dfs, F statistics, P values, and effect sizes (ηp2) are reported in each column. Initiation costs were calculated for each participant by subtracting the mean RTs and ERs at position 1 from position 3. Sequence costs were calculated per participant by subtracting the averaged RTs and ERs in complex from simple sequences. Switch costs were calculated for each participant by subtracting the mean RT and ER across all repeat trials (pooled complex position 3, simple positions 2 and 4) from the mean RT and ER across all switch trials (pooled complex positions 2 and 4, simple position 3).

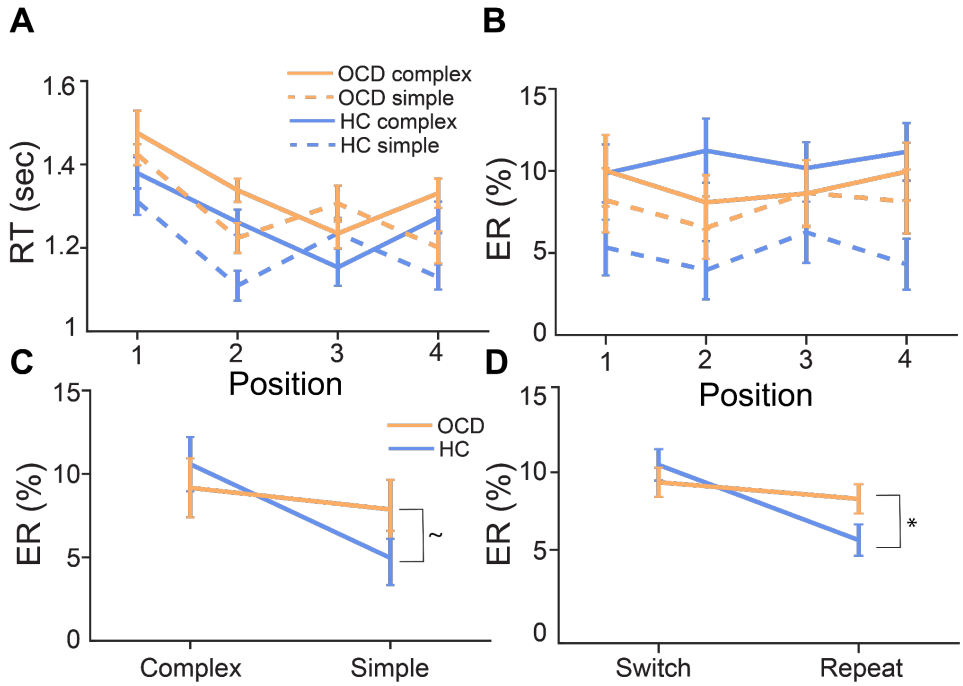

Figure 2. Behavioral differences occur in ERs between HCs and OCD. A. RTs between HCs and OCD do not significantly differ across simple and complex sequences. **B**. ERs significantly differ between HCs and OCD across sequence positions. **C**. There is a marginal interaction in ERs by sequence type (complex vs. simple) between groups (indicated by "~"). **D.** There is a significant interaction in ERs by trial type (switch vs. repeat trials) between groups (indicated by "*").

Since we observed behavior deficits in ERs in the current study, we next tested if these behavioral deficits in OCD correlated with clinical measures. Specifically, we assessed if and how ER sequence and switch costs correlated with four clinical measures: OCD symptom severity (total Y-BOCS scores), anxiety (OASIS and DASS anxiety subscale), and depression (DASS depression subscale). A previous study reported a positive correlation between OCD symptom severity and deficits in cognitive control (Remijnse et al., 2013). Clinical measures of anxiety and depression were investigated because of the high rates of comorbidity of anxiety and depression diagnoses with OCD (Sharma et al., 2021), as well as a previous behavioral study conducted by our research group which observed deficits on this sequential task in participants with anxiety disorders (Doyle, Boisseau, Garnaat, Rasmussen, & Desrochers, 2024). We found that ER sequence and switch costs correlated marginally with OCD symptom severity and

significantly with anxiety and depression (**Figure 3A-D**; ER sequence cost: Y-BOCS p = 0.05, r = 0.38; OASIS p = 0.03, r = 0.45; DASS anxiety p = 0.01, r = 0.51; DASS depression p = 0.02, r = 0.4; ER switch cost: Y-BOCS p = 0.06, r = 0.38; DASS depression p = 0.01, r = 0.5; DASS anxiety p = 0.01, r = 0.49, OASIS p = 0.02 r = 0.48), such that high costs correlate with higher symptom severity. In other words, OCD participants with higher symptom severity scores exhibited greater sequence and switch costs.

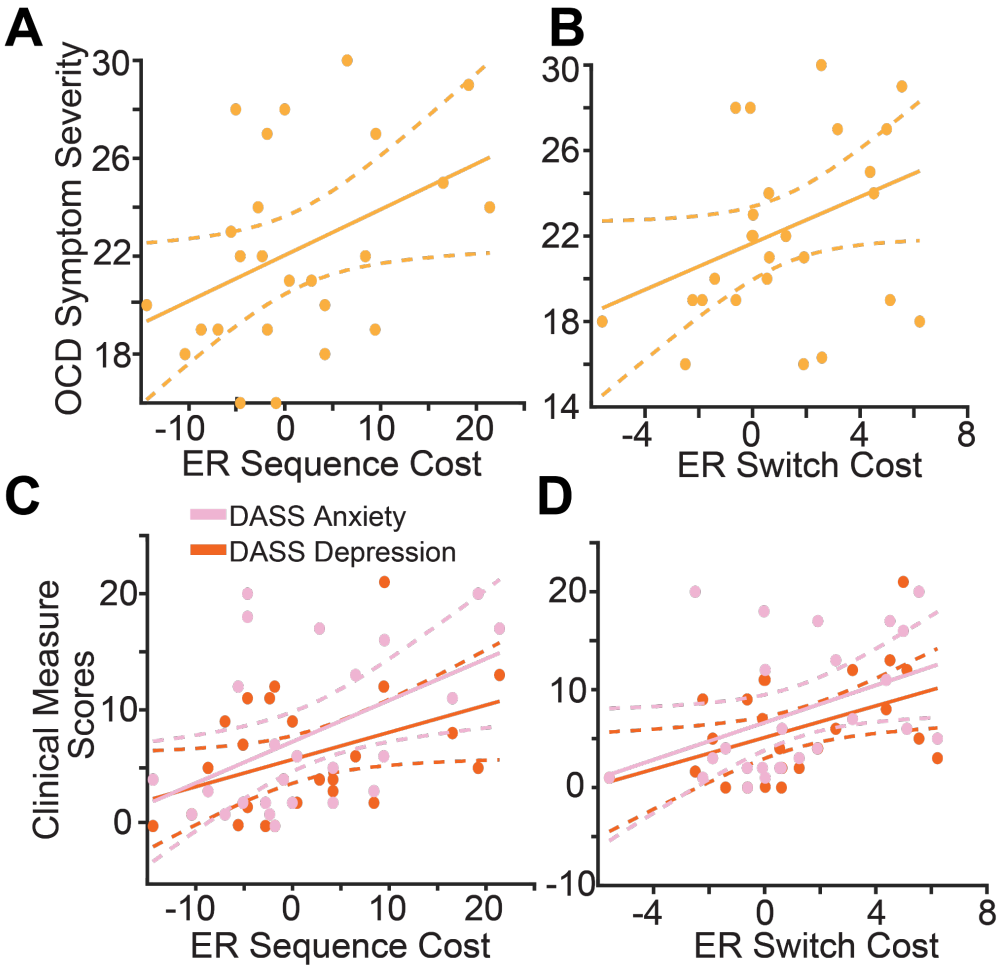

Figure 3. ER sequence and switch costs correlate with symptom severity in OCD. A. OCD symptom severity (total Y-BOCS) significantly correlates with ER sequence cost. **B.** OCD symptom severity significantly correlates with ER switch cost. **C**. Clinical measures (anxiety [DASS anxiety subscale] and depression [DASS depression subscale]) significantly correlate with ER sequence cost. **D**. Clinical measures (anxiety [DASS anxiety subscale] and depression [DASS depression subscale]) significantly correlate with ER switch cost. Solid lines indicate lines of best fit, and dashed lines indicate confidence intervals.

Onset activity does not dissociate OCD from HCs but correlates with clinical measures

Since the present behavioral task was used in a previous neuroimaging study in HCs (Desrochers et al., 2015), we first sought to replicate effects related to general and sequential cognitive control. We examined neural responses to task switching as an indicator of general cognitive control (Monsell, 2003) and a specific neural dynamic, increasing activation across items in each sequence ("ramping"), as an indicator of sequential control. Ramping dynamics have been shown to be robustly associated with a variety of sequential tasks (Desrochers et al., 2015, 2019). First, to test for neural activity related to task switching, we created ROIs from regions previously observed to have significant switch > repeat neural activity (Desrochers et al., 2015) (see Methods). We found significant or marginal activity across all participants in the majority of ROIs in these conditions (L occipital: $t(49) = 3.16$, $p < 0.001$, R IFG [No Position 1 Switch > Repeat]: $t(49) = 1.83$, $p = 0.05$, R SMA/cingulate: $t(49) = 1.71$, $p = 0.06$, R IFG [Position 23 Switch > Position 23 Repeat]: $t(49) = 2.03$, $p = 0.04$). Activity related to task switching was not significantly different between OCD and HCs in any of the ROIs ($t(48) = -1.02$, $p = 0.5$, all ROIs combined), replicating neural responses to task switching.

Second, to initially examine ramping dynamics in this population of participants, we first aimed to replicate the existence of a distribution of brain areas that show this dynamic during the task. Ramping was modeled as a parametric increase in BOLD activation across the four positions of each sequence (i.e., resetting at position 1) that explained variance above and beyond stimulus onsets. Though we had hypotheses about the involvement of specific regions in this task (i.e. the RLPFC), we first wanted to establish the general presence of ramping activation. To test for this activity, we created a single large ROI that contained all the significant ramping clusters from the All Parametric > Baseline contrast in (Desrochers et al., 2015). We found significant ramping activity in this combined ROI in each group separately (OCD: $t(24) = 2.98$, $p = 0.001$, HC: $t(24) = 3.39$, $p = 0.002$), and no difference in ramping between groups ($t(48) = -0.14$, $p = 0.88$), replicating neural effects of general cognitive and sequential control in OCD and HC groups in this study.

Having replicated neural responses to general cognitive and sequential control we next tested hypotheses related to the overall level of activation in key frontal cortical regions and the potential correlation with symptom severity. Previous studies observed hypoactivation of prefrontal cortical regions, such as dorsolateral PFC (DLPFC), in OCD during cognitive control tasks (Gu et al., 2008) which correlated with symptom severity (Remijnse et al., 2013). A region of the PFC that is interconnected with the DLPFC (Shekhar & Rahnev, 2018) and necessary for sequential control (Desrochers et al., 2015) is the RLPFC. Given the central role of RLPFC in sequential processing in healthy individuals, we hypothesized that decreased overall RLPFC activity in this task would correlate with symptom severity in OCD. To create an RLPFC ROI to use in testing this hypothesis, we again used a region of significant activation from this previous study. Though we were not addressing ramping activation in this particular hypothesis test, the most relevant definition of RLPFC as related to the performance of a sequential task was the cluster of significant ramping activation in left RLPFC in the (Desrochers et al., 2015) study. This region, hereafter referred to as the D15 ROI, is the same region that stimulation of, using transcranial magnetic stimulation (TMS), selectively produced task deficits in HCs (Desrochers et al., 2015). Using the D15 ROI, we found no significant difference in overall (onset) activity (using the All > Baseline contrast) between the groups (**Figure 4A**; $t(48) = -1.12$ $p = 0.27$). However, we observed a significant positive correlation between overall task activity in RLPFC

and OCD symptom severity (total Y-BOCS score) (**Figure 4B**; p = 0.037, r = 0.43). We therefore did not find evidence for decreased RLPFC activity in OCD but observed a relationship between OCD symptom severity and RLPFC activity.

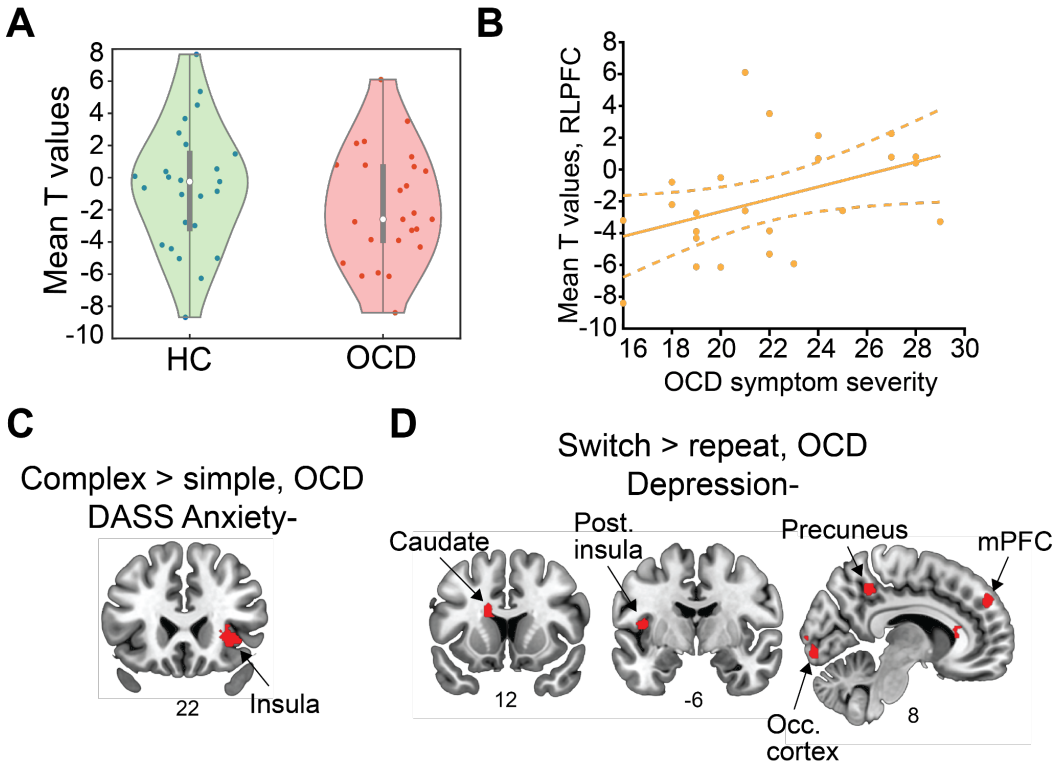

Figure 4. All > Baseline during the sequence task in OCD vs. HCs and correlations with symptom severity. A. All > BaselineOverall activity and ramping activity in RLPFC ROI in HCs vs. OCD. **B**. OCD symptom severity (total Y-BOCS scores) correlation with All > Baseline activity activity in RLPFC in OCD. **C.** Anxiety measures (OASIS and (DASS anxiety) correlates with onset neural activity in the insula in Complex > Simple sequences in OCD (family wise error [FWE] cluster corrected for multiple comparisons at P, $p < 0.05$, height threshold at $P < 0.001$, extent threshold 167 voxels). **D.** Depression (DASS depression) correlates with onset neural activity during Switch > Repeat trials in OCD (FWE cluster corrected at P, $p < 0.05$, height threshold at $P < 0.001$, extent threshold 130 voxels).

We followed up these ROI analyses with brain-wide correlations between neural activity and clinical measures to explore the involvement of brain regions outside of the RLPFC. The set of contrasts and clinical measures chosen was motivated by the aforementioned D15 correlation with OCD symptom severity and the observation that ER sequence and switch costs correlated with OCD symptom severity, anxiety, and depression measures (**Figure 3**). Specifically, we examined overall onset activity (All > Baseline), neural sequence cost (activity in Complex > Simple sequences), and switch cost (activity in Switch > Repeat trials) with OCD symptom severity (total Y-BOCS scores), anxiety (DASS anxiety subscale and OASIS), and depression (DASS depression subscale) measures. There were no significant clusters that correlated with OCD symptom severity across any of the three contrasts examined: All > Baseline, Complex > Simple, or Switch > Repeat. Anxiety measures showed significant clusters of correlation with activity in Complex > Simple in the right inferior frontal gyrus and insula cortex (**Figure 4C** shows DASS anxiety correlation with insula activity**; Table 2**), but not with All > Baseline or Switch > Repeat. However, severity of depressive symptoms showed significant clusters of

correlated activity in Switch > Repeat trials in the caudate, precuneus, posterior insula, medial PFC, and occipital cortex (**Figure 4D**; **Table 2**), but not in All > Baseline or Complex > Simple. In summary, correlations were observed between sequence related neural activity (Complex > Simple) and anxiety, and more general cognitive control (task switching) neural activity correlated with depressive symptoms in different sets of brain areas. These results suggest that symptomatology may load on different networks of brain areas during general cognitive compared to sequential control in OCD.

Contrast Location	BA	Extent (voxels)	*x*	*y*	*z*	*Peak t-val.*
Simple > Complex (OASIS+)						
IFG pars triangularis	45	193	46	30	2	5.07
Frontal operculum	47		46	22	-4	4.28
Simple > Complex (DASS anxiety+)						
Anterior insula	47	175	32	26	-2	4.84
Anterior insula	47		30	24	8	4.3
Anterior insula	48		22	16	4	4.19
Repeat > Switch (DASS depression+)						
Anterior medial prefrontal cortex	9	174	6	52	38	4.82
Ant. medial prefrontal cortex/dorsal ACC	9		16	48	30	4.49
Putamen	NA	294	-14	12	22	7.32
Middle cingulate gyrus	32		-14	22	20	6.11
Anterior cingulate gyrus	25		10	26	12	4.43
Anterior cingulate gyrus	25		-12	32	8	4.34
putamen	NA		-18	4	24	4.3
Anterior cingulate gyrus	25		18	26	18	3.97
Posterior insula	48	185	-34	-20	6	5.68
Anterior insula	48		-40	-8	8	5.56
Transverse temporal gyrus	41		-36	-32	8	5.08
Central operculum	48		-42	2	8	3.98

Precuneus	23	147	14	-44	44	5.86
Precuneus	23		-4	-46	42	3.95
Posterior cingulate	23		16	-38	38	3.9
Precuneus	23		-14	-46	40	3.88
Lingual gyrus	18	154	10	-90	-8	5.56
Cuneus	18		4	-94	8	4.73

Table 2. Activation coordinates, significant neural activity correlated with anxiety (OASIS and DASS anxiety subscale) and depression (DASS depression subscale). Clusters reliable at $P < 0.05$ corrected. Coordinates are the center of mass in MNI. Clusters are reported for peaks of activation 12 mm or greater distance apart.

Cortical ramping dynamics dissociate OCD from HCs to support abstract sequential behavior

After examining onset activity to test hypotheses related to potential hypoactivation in OCD during sequential tasks, we next tested the hypotheses related to ramping dynamics. BOLD activity that ramps (increases) over the four positions in the sequence and resets at the first position has previously been shown to be necessary for abstract sequential task performance in HCs (Desrochers et al., 2015). Individuals with OCD can exhibit dysfunctional naturalistic abstract sequential behavior, which implicates differential ramping dynamics potentially underlying these behaviors in this clinical population. As in our examination of onset activity, we tested hypotheses about potential deficits in ramping activity in OCD in an RLPFC ROI, the whole brain, and its relationship to behavioral costs.

We first tested our hypothesis that decreased RLPFC ramping in OCD compared to HCs correlates with symptom severity, as onset activity did in All > Baseline. Using the D15 ROI, there was not a significant difference in RLPFC ramping between groups (**Figure 5A**; $t(48) = -0.36$, $p = 0.72$), and there was no correlation between OCD symptom severity and ramping activity in RLPFC (**Figure 5B**; $r = -0.03$, $p = 0.90$). These results show no differences in RLPFC dynamics between groups, contrary to our hypothesis.

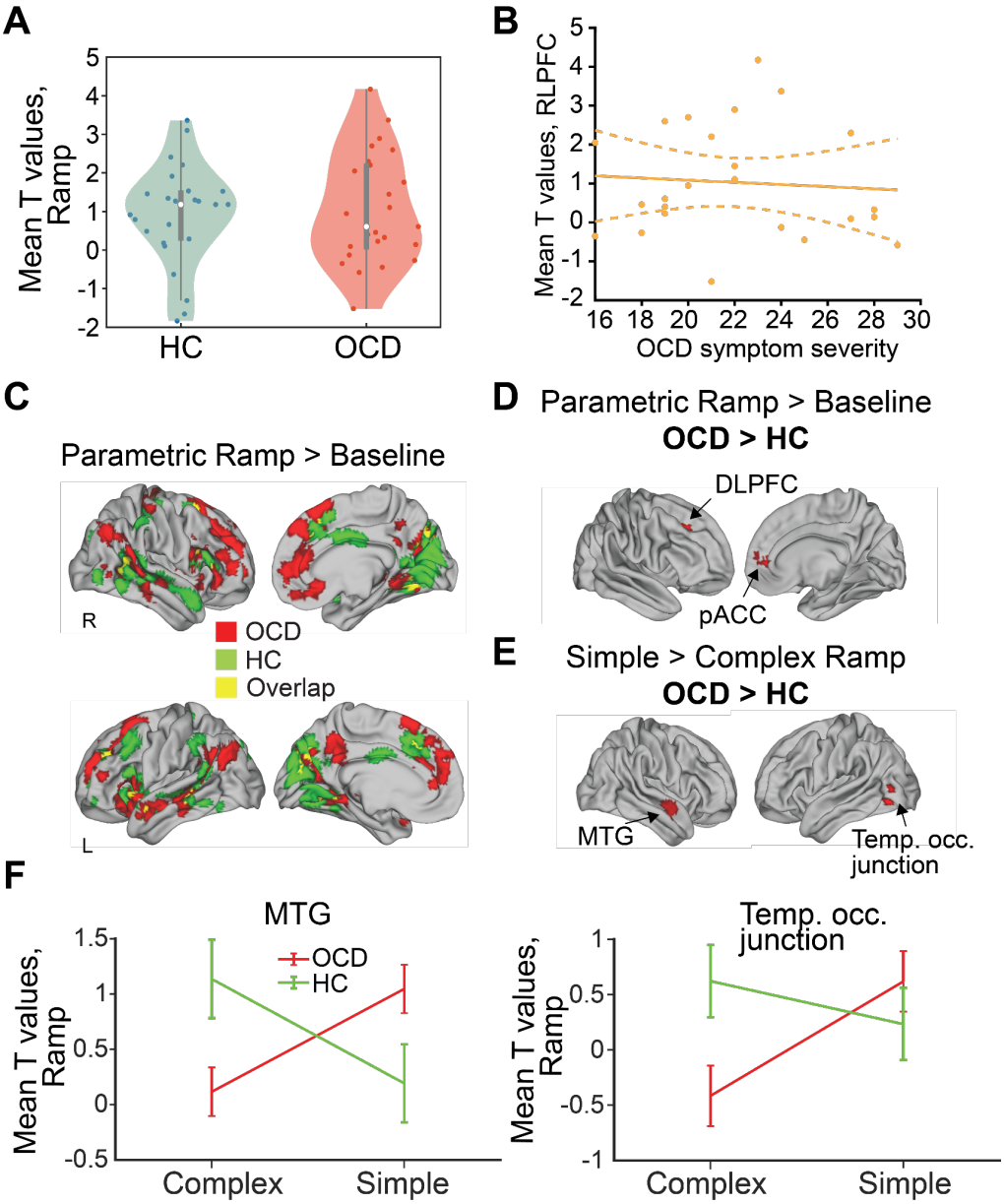

Figure 5. Ramping activity in novel cortical regions but not RLPFC dissociates groups in the whole brain. A. Ramping activity in the D15 ROI does not differ between HCs and OCD. **B**. OCD symptom severity (total Y-BOCS scores) does not significantly correlate with D15 ROI ramping in OCD. **C**. Whole brain contrast All > Baseline, Ramp, FWE cluster correct at $P < 0.05$, height threshold $P < 0.001$, extent threshold 235 voxels. HCs activity shown in green, OCD shown in red, yellow is overlap. **D.** All > Baseline Ramp, FWE cluster corrected at $P < 0.05$, height threshold $P < 0.005$, extent threshold 167 voxels, OCD > HC, ramping activity that is present in OCD but not in HCs. **E**. Simple > complex, ramp, FWE cluster corrected at $P < 0.05$, height threshold $P < 0.001$, extent threshold 136 voxels, OCD > HC, ramping activity during simple compared to complex sequences that is present in OCD but not in HCs.

Results from whole-brain contrasts of ramping supported the ROI results, and revealed new regions that dissociated the groups. Previous studies showed that multiple areas outside of the RLPFC also showed ramping dynamics during abstract task sequences (Desrochers et al., 2015, 2019). Building on the observation that both groups had significant ramping activity across the brain that aligned with previous results (see paragraphs on replication at the start of

this section), we first examined potential overlap of ramping activity in the All Parametric Ramp > Baseline contrast between groups. Though there was some overlap (**Figure 5C**, yellow; **Table 3**), many areas of significant ramping activation did not overlap. To directly test for ramping differences between OCD and HC, we used the All Parametric Ramp OCD > All Parametric Ramp HC contrast. This contrast showed significant OCD > HC ramping in the pregenual anterior cingulate cortex (pACC) and superior frontal sulcus (SFS), a region of DLPFC (**Figure 5D**; **Table 3**). These regions have previously been implicated in OCD (Hollunder et al., 2024; Shephard et al., 2021), but not through investigation of ramping dynamics (see Discussion). No clusters of activation survived correction in the reverse, HC > OCD ramping contrast. We therefore observed novel dynamics in prefrontal cortical regions that differentially support abstract sequential behavior in OCD compared to HCs.

Contrast Location	BA	Extent (voxels)	*x*	*y*	*z*	*Peak t-val.*
Ramp > Baseline						
HC						
RLPFC	46,10	244	-32	52	-8	4.59
IFG pars opercularis	45	306	56	26	10	5.86
anterior insula	47	1182	-34	22	-6	6.31
IFG pars opercularis	45		-50	18	14	5.72
Superior temporal gyrus	21		-52	4	-12	4.34
Middle cingulate gyrus	24	2751	6	6	30	6.48
Dorsal anterior cingulate cortex	32		-2	28	42	5.58
Middle frontal gyrus	44		-48	24	36	5.4
DLPFC	46		-22	38	28	5.26
Supplementary Motor Area (SMA)	8		-26	20	56	4.69
Supplementary Motor Area (SMA)	8		24	14	52	4.63
Middle cingulate gyrus	24		-8	-18	36	4.18
Primary motor cortex (M1)	4	1012	26	-26	54	6.14
Supramarginal gyrus	40		48	-34	40	5.17
Primary Somatosenesory cortex	3	153	-22	-30	58	5.38
Middle temporal gyrus	21	750	-52	-32	-6	5.4
Auditory cortex	41		-40	-46	12	4.21
MTG and Wernicke's area	21		-64	-52	8	3.6

Cerebellum exterior	30	150	-12	-44	-24	5.76
Supramarginal gyrus	40	324	-52	-44	42	5.15
V1	17	9920	-12	-68	14	7.81
V1	17		14	-64	12	7.07
Middle temporal gyrus	21		48	-28	-6	6.96
Middle temporal pole	38		48	12	-20	6.73
Poster middle temporal gyrus	21		68	-48	2	6.54
V2	18		20	-78	32	6.41
Cerebellum exterior	30		-10	-60	-22	5.63
Superior parietal lobule	7		-12	-74	44	5.33
Fusiform gyrus	37		-34	-64	-10	5.24
Lateral occipital gyrus	19		48	-76	2	4.94
Cerebellum exterior	30		16	-62	-14	4.62
Cerebellum exterior	30		-34	-62	-36	4.33
Cerebellum exterior	30		34	-70	-30	4.02
OCD						
Orbitofrontal cortex	11	191	10	22	-8	5.54
Orbitofrontal cortex	11		6	46	-16	4.51
Frontal operculum	47	1350	-46	20	2	6.18
Anterior middle temporal gyrus	38		-34	18	-22	5.8
Middle temporal gyrus	22		-50	-8	-12	5.02
IFG pars opercularis	44	7891	30	16	34	7.79
DLPFC	9		-22	24	34	6.59
Supplementary motor area	6		14	14	56	6.56
IFG pars triangularis	45		56	28	2	5.81
RLPFC	10		-16	52	14	5.8
DLPFC/dorsal ACC	32		18	42	26	5.71
Superior frontal gyrus	8		-22	16	58	5.36
Frontopolar prefrontal cortex	10		14	54	4	5.17

IFG pars opercularis	44	711	50	12	24	5.41
Anterior insula	48		30	18	-8	4.34
Superior temporal gyrus	22	2202	54	-16	-8	5.26
Posterior middle temporal gyrus	21		56	-48	4	5.1
Primary motor cortex (M1)	6		26	-20	64	4.95
Supramarginal gyrus	48		46	-36	28	4.85
Primary somatosensory cortex	1		50	-28	56	4.21
Middle temporal gyrus	48	1764	-42	-26	-4	7.22
Angular gyrus	39		-56	-56	30	5.24
Angular gyrus	19		-34	-78	40	4.2
Middle temporal gyrus	20		-64	-30	-16	4
Lingual gyrus	30	573	-16	-42	-12	5.73
Lingual gyrus	30	787	26	-48	-4	6.04
Precuneus	23	668	-10	-50	42	5.56
Angular gyrus	39	222	48	-64	36	5.12
Cerebellum exterior	NA	889	-24	-70	-38	5.96
Cerebellum exterior	NA		-46	-54	-36	3.57
Cerebellum exterior	NA	716	36	-76	-34	6.26
Cerebellum exterior	NA		44	-52	-44	3.62
Cuneus	18	1515	-6	-76	32	4.75
Precuneus	18		22	-64	24	4.51
Lingual gyrus	19		-22	-54	8	3.59
OCD > HC						
Supplementary motor area	32	822	20	18	38	5.25
DLPFC	48		22	18	28	4.27
DLPFC	48		26	14	22	4.13
DLPFC	48		26	36	14	4.05
DLPFC	48		24	26	36	3.75
IFG pars operculum	48		30	8	18	3.65
Precentral gyrus	48		36	4	22	3.54

Anterior cingulate cortex	32	14	44	6	3.51
Anterior medial prefrontal cortex	10	14	56	8	3.38
DLPFC	48	26	28	22	3.34
Frontal operculum	48	40	12	16	3.19
Supplementary motor area	6	28	8	38	3.16
Central operculum	48	46	4	8	2.92

Table 3. Activation coordinates, significant ramping activity in the Ramp > Baseline contrast in HC, OCD, and OCD > HC. Clusters reliable at $P < 0.05$ corrected. No clusters in the HC > OCD Ramp > Baseline contrast survived correction. Extent threshold $P < 0.001$ for the OCD and HC contrasts, and $P < 0.005$ for the OCD > HC contrast. Distance between significant clusters was set to 25 mm for the HC and OCD contrasts. Distance between significant clusters was set to 12 mm for the OCD > HC contrast. Coordinates are the center of mass in MNI.

Because we observed behavioral differences in sequence costs between the groups (**Figure 2C**), we reasoned that there could be differences in this key, sequence related ramping dynamic across the sequence types. To test if ramping is significantly different in sequence cost, we compared the Simple > Complex Parametric Ramp contrast in OCD > HC. Ramping activity in OCD was significantly increased in a region of the medial temporal cortex and the temporo-occipital junction compared to HCs (**Figure 5E**; **Table 4**). There were no clusters that reached statistical significance in the reverse HC > OCD contrast. However, we observed the same clusters of increased ramping in HC > OCD in the Complex > Simple Parametric contrast (**Table 4**; not shown in **Figure 5** because clusters are identical to **Figure 5E**). The ramping in these contrasts resulted in an interaction in ramping by sequence type between groups in both clusters (biased clusters based on areas of significant activation used to illustrate the interaction, **Figure 5F; Table 4**). Thus, differences in ramping activity generally align with differences in behavioral performance for different sequence types when comparing OCD to HC and reveal ramping in novel regions in HCs during this task.

Contrast Location	BA	Extent (voxels)	*x*	*y*	*z*	*Peak t-val.*
Simple > Complex Ramp						
OCD						
Inferior occipital gyrus	19	457	-36	-72	-4	5.08
V2	18		-24	-78	2	3.89
Inferior temporal gyrus	37		-38	-56	-2	3.59
Middle occipital gyrus	37		-42	-72	8	3.27
OCD > HC						
Superior temporal gyrus	22	1099	58	-4	-10	4.77

Superior temporal gyrus	22		68	-20	6	4.06
Planum temporale (Wernicke's area)	22		54	-24	8	3.64
Middle temporal gyrus	20		48	-20	-12	3.52
Temporal pole	38		54	12	-22	3.42
Temporal pole	38		42	8	-40	3.34
Superior temporal gyrus	22		64	-14	-4	3.29
Middle temporal gyrus	21		48	-38	2	2.93
Primary motor cortex	6	405	20	-14	66	3.95
Primary motor cortex	6		30	-24	64	3.27
Primary motor cortex	6		18	-26	66	3.21
Supplementary motor area	6		12	-8	58	3.15
Primary somatosensory cortex	3		46	-22	54	2.95
Lateral occipital gyrus	19	614	-36	-72	-4	4.33
Temporo-occipital junction	37		-42	-72	8	3.88
Lateral occipital gyrus	18		-24	-78	8	3.19

Table 4. Activation coordinates, significant ramping activity in the Simple > Complex, Ramp contrast in OCD and OCD > HC. Clusters reliable at $P < 0.05$ corrected. No clusters in the HC and HC > OCD Simple > Complex Ramp contrast survived correction. Clusters in the HC > OCD Complex > Simple Ramp were the exact same as those in the OCD > HC Simple > Complex Ramp and were not reported for simplicity. Extent threshold $P < 0.005$ was used for both the OCD and the OCD > HC contrasts. Distance between significant clusters was set to 12 mm. Coordinates are the center of mass in MNI. Extent threshold $P < 0.001$ for the OCD and HC contrasts.

Anxiety and depressive symptoms mediate the relationship between neural activity and behavior in OCD

Across several sets of results, we observed correlations between clinical measures and both behavior and neural responses. We originally hypothesized sequential behavior deficits would correlate with clinical measures in OCD. In support of this hypothesis, anxiety and depression correlated with ER sequence and switch cost deficits. Anxiety correlated with onset neural activity during Simple > Complex sequences and depression correlated with onset activity during Repeat > Switch trials. These results, therefore, raise the possibility that these clinical measures influence the relationship between neural activity and behavior. We therefore examined these effects in a formal mediation analysis. We hypothesized that for each behavioral and neural correlation, the clinical measure would reduce the effect that activity directly has on behavior (**Figure 6A**; see Methods for details). The mediation analyses consisted of three stepwise linear models to assess the following relationships: the first assessed the direct effect of neural activity on behavior, the second assessed the effect of the clinical measure scores on

behavior, and the third assessed the combined effects of the scores and activity on behavior. We performed these analyses for two sets of relationships in OCD: Complex > Simple onset activity with ER sequence cost, and Switch > Repeat onset activity with ER switch cost.

We first tested if anxiety scores mediated the relationship between onset activity in Complex > Simple sequences and ER sequence cost. This test was motivated by our previous result showing that anxiety measures correlated with sequence cost (**Figure 3C**) and with neural activity by sequence type (**Figure 4C**). The first linear model showed that the observed neural correlates of anxiety (**Figure 4C** and **Table 2**) also significantly correlated with ER sequence cost, the second showed that anxiety scores (OASIS and DASS anxiety subscale) correlated with neural activity in Complex > Simple sequences, and the third showed that anxiety severity reduces the effect of Complex > Simple activity on ER sequence cost (**Table 5**, **rows 1-2**). These results are considered a partial mediation (MacKinnon, Fairchild, & Fritz, 2007). To determine if this partial mediation was unique to anxiety severity, we tested if depressive symptoms similarly mediated the relationship between Complex > Simple activity and ER sequence cost. We found that depressive symptom severity partially mediated the relationship between Complex > Simple activity and ER sequence cost (**Table 5**, **row 3**), but to a lesser extent than anxiety scores. Therefore, we provide evidence for a partial dissociation and partial mediation of neural activity and behavior by anxiety in an abstract sequential task in OCD (**Figure 6B**).

We next tested if depressive symptoms mediated the relationship between onset activity in Switch > Repeat trials and ER switch cost. This analysis was motivated by the result that depressive symptoms (DASS depression) correlated with switch cost (**Figure 3D**), and with neural activity during task switching (**Figure 4D** and **Table 2**). The first linear model showed that all the observed neural correlates of depressive symptoms (**Figure 4D** and **Table 2**) except mPFC activity (not shown in **Table 5**) also correlated with ER switch cost in OCD, the second showed that depressive symptoms correlated with neural activity in Switch > Repeat trials in OCD, and the third showed that depressive symptoms reduces the effect of Switch > Repeat activity on ER switch cost (**Table 5, rows 4-7**). Three neural correlates of depressive symptoms (caudate, posterior insula, and occipital cortex activity) resulted in a full mediation effect, such that the total effect from incorporating depressive severity into the linear model results in insignificance (**Table 5**, **rows 4-6**). The last mediation analysis (**Table 5, row 7**) showed a partial mediation. To determine if depressive severity was a unique mediator, we tested if anxiety similarly mediated the relationship between Switch > Repeat activity and ER switch cost. We found that anxiety severity (both OASIS and DASS anxiety scores) did not significantly correlate with neural correlates of depressive symptoms and thus did not mediate the relationship between Switch > Repeat activity and ER switch cost. Therefore, we show depressive symptoms mediated the relationship between task switching neural activity and behavioral switch cost.

Model:	**Direct effect**	**Indirect effect**	**Total effect**
ER sequence cost ~ DASS anxiety + Insula activity	0.36 (0.002)	3.0 (< 0.001)	0.31 (0.05)
ER sequence cost ~ OASIS + IFG activity	0.38 (0.001)	1.4 (< 0.001)	0.32 (0.04)
ER sequence cost ~ DASS depression + IFG activity	0.38 (0.001)	1.66 (0.02)	0.33 (0.01)

ER switch cost ~ DASS depression + Caudate activity	-0.52 (0.02)	-4.35 (< 0.001)	-0.33 (0.29)
ER switch cost ~ DASS depression + Post. Insula activity	-0.36 (0.05)	-3.10 (<0.001)	-0.17 (0.46)
ER switch cost ~ DASS depression + Occ. cortex activity	-0.44 (0.01)	-2.52 (0.004)	-0.32 (0.10)
ER switch cost ~ DASS depression + Precuneus activity	-0.37 (0.005)	-2.20 (0.001)	-0.30 (0.06)

Table 5. Table depicting mediation analyses. Left hand column depicts the full linear model (3rd in the series of 3 in the mediation analyses) showing the effect of clinical measure scores on the relationship between neural activity and behavior. The direct effect shows the estimate (p-value) from the 1st linear model behavior~neural activity. The indirect effect reports the estimate (p-value) from the 2nd linear model behavior~clinical measure scores. The total effect shows the estimate (p-value) on the neural activity in the 3rd model, behavior~clinical measure scores + neural activity, which is described in the first column**.** A reduced estimate and lessened significance in the 'total effect' column compared to the estimate and p-value in the 'direct effect' column indicates partial mediation by the clinical measure scores. An insignificant p-value in the 'total effect' column compared to the p-value in the 'direct effect' column indicates full mediation.

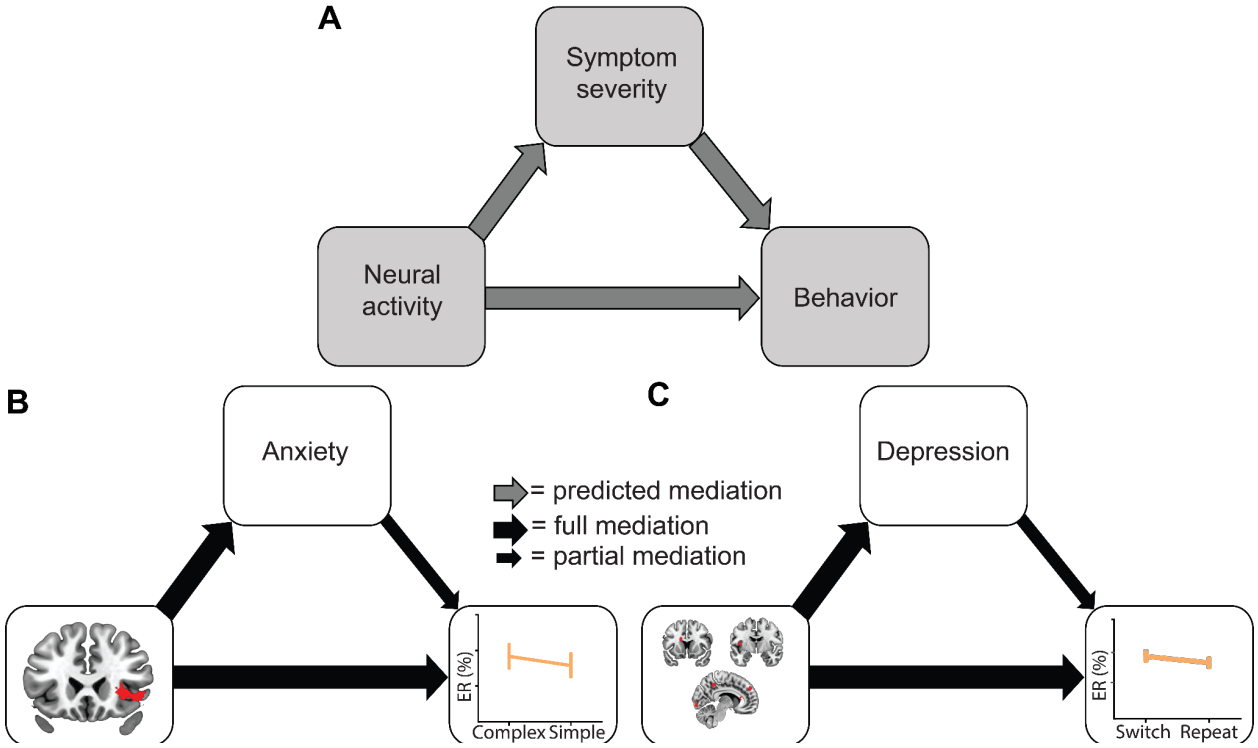

Figure 6. General prediction for mediation analyses and illustration of results that show clinical measures mediate brain-behavior relationships in OCD. Arrows between symptom severity (mediator) and behavior (outcome) represent strength of predicted (A) or observed (B and C) mediation effects. **A.** General prediction that symptom severity mediated the relationship between neural activity with behavior during the sequence task. **B.** Schematic showing anxiety scores (OASIS and DASS anxiety) partially mediated the relationship between onset activity in Complex > Simple sequences and ER sequence cost (narrower arrow between 'Anxiety' and 'ER

sequence cost' compared to equivalent arrow in **A**). **C.** Schematic showing depression scores (DASS depression) partially mediated the relationship between onset activity in Switch > Repeat trials and ER switch cost (narrower arrow between 'Depression' and 'ER switch cost' compared to equivalent arrow in **A**).

Discussion

We investigated abstract sequence behavior and its neural correlates in OCD using fMRI. We found that participants with OCD exhibited behavioral deficits in ER sequence and switch costs compared to HC. We did not observe hypoactivation in RLPFC onset activity as hypothesized due to potential involvement in the CTSC circuitry. We also hypothesized that RLPFC ramping dynamics would be altered in OCD because of their necessity for abstract task sequence performance. We did not observe any difference between OCD and HC RLPFC ramping. However, novel cortical areas, DLPFC and pACC showed increased ramping activity in OCD compared to HCs. We also found that severity of anxiety and depressive symptoms mediate the relationship between activation and observed ER behavior deficits. In summary, our findings suggest that cortical regions, in addition to RLPFC, were recruited to support abstract sequence behavior in OCD, and that symptom severity mediates the relationship between neural activity and task accuracy. Our work suggests expansion of neurobiological models of cognitive control dysfunction in OCD to include the specific regions of DLPFC/pACC observed in our study and may provide novel target regions in future TMS treatments.

Our ramping results highlight pACC and SFS/DLPFC as part of circuitry underlying cognitive control dysfunction in OCD. We did not observe DLPFC hypoactivity in OCD during our task, as predicted by previous cognitive control studies that report this relationship (Fremont et al., 2022; Gu et al., 2008). Further, we did not observe decreased activity or ramping in RLPFC as hypothesized, which does not implicate this region in established CSTC models. However, we show increased pACC and SFS activity during sequential behavior in OCD with ramping, a novel dynamic. One study highlights the relevance of the pACC in OCD by showing that ventral posterior thalamic nucleus sites that are stimulated as treatment project to this region (Hollunder et al., 2024). This work implicates specific subregions of the broader CSTC, with one of these mapping onto the area of ramping observed in the current study. In concordance with this study, our work delineates specific subregional CSTC circuitry to inform broader models of cognitive control in OCD. Further, regions of the SFS are already implicated as part of the dysfunctional dorsal cognitive circuit (Shephard et al., 2021), and our work highlights a specific subregion relevant to cognitive control that may be incorporated into this circuit, with potential relevance to neuromodulatory interventions for OCD treatment (Dunlop et al., 2016; Fitzsimmons et al., 2022; Harmelech et al., 2022). Therefore, our results highlight the utility in investigating ramping as a relevant dynamic and suggest biological models should incorporate these specific cortical and connected subcortical subregions as circuitry implicated as dysfunctional during cognitive control in OCD.

Ramping in additional cortical regions may serve as potential compensatory mechanisms to support abstract sequential behavior in OCD. Specifically, our results showed OCD participants recruit additional brain regions (MTG and temporo-occipital junction) during complex compared to simple sequences. We observed increased ramping in a region of MTG, regions in which has also previously been associated with the sequence memory of episodic events (Leshinskaya & Thompson-Schill, 2020; Tubridy & Davachi, 2011). This MTG region is also functionally connected to the ventromedial PFC and precuneus, regions that have been shown to be dysfunctional during complex cognitive processing in OCD (Stern et al., 2011).

Further, the temporo-occipital junction is active in response to the spatial frequency of visual images (Jakobs et al., 2009), a feature inherent to many types of visual sequential tasks. In addition to our results, previous studies support the recruitment of these regions for sequential behavior and their involvement in OCD pathology. In our current paradigm, increased ramping in these regions may compensate for dysfunctional connected regions and be recruited to support sequential control during the task. In OCD, these regions may serve as compensatory mechanisms to support abstract sequential control. Based on connectivity of these regions and our ramping results, these areas of activation may be crucial for abstract sequences in OCD.

Our findings raise the question of whether behavioral deficits on this task may be transdiagnostic. In a previous behavioral study, participants performed the same abstract sequence task, but with different timing between the trials (and not in the scanner) (Doyle et al., 2024). There were three groups: participants with a primary OCD diagnosis who did not have anxiety disorders (OCD), participants with a primary diagnosis of an anxiety disorder who did not have OCD (ANX), and HCs. ANX participants showed behavioral deficits in RTs on the abstract sequence task that dissociated from participants with OCD and HCs, who did not show deficits. These apparent differences in behavioral results between the OCD group in our previous study and current study could be attributed to differences in the intertrial intervals necessary for performance during fMRI scanning. Inter trial intervals in the previous study were always 0.5 s, compared to the current study where they were jittered (0.25 - 8 s, mean 2 s). These longer and more variable intertrial intervals could lead to increased uncertainty during a cognitive task (Jakobs et al., 2009), a process demonstrated to be impaired in OCD (Pinciotti, Riemann, & Abramowitz, 2021). Additionally, anxiety levels in the OCD population could be increased during scanning, a correlation established previously (Katz, Wilson, & Frazer, 1994; McIsaac, Thordarson, Shafran, Rachman, & Poole, 1998). However, as anxiety disorders and OCD are clinically similar, behavioral deficits in these groups in abstract sequences may be intertwined. This relationship is further complicated by the observed neural correlations with anxiety and depression (**Figure 4C, D**), which show these symptoms load on distinct brain regions during different task conditions. Further studies are needed to explicate potentially distinct behavioral deficits and their neural correlates during abstract sequences in these two closely related disorders.

Potential limitations to this study are due to sample size, diagnostic measures, and the need for comparison to other clinical populations. Our sample contained a heterogeneous population of individuals with OCD, which limited our ability to assess subtypes and symptom dimensions. Further, the present study included individuals with comorbid anxiety diagnoses, which are common in OCD, and did not contain a direct comparison for anxiety disorders to replicate behavior observed using this task previously (Doyle et al., 2024) and to further assess the role of anxiety in behaviorally and neurally in OCD compared to anxiety disorders. However, we note that despite a small sample size, we observed robust significant ramping activity in OCD compared to HCs, results which may be used to further probe the role of pACC and SFS/DLPFC and for future connectivity analyses to investigate contributions of networks involved in supporting abstract sequencing in OCD. Similarly, future studies can incorporate larger populations to accommodate the investigation of a wider array of groups and accompanying diagnoses.

Here, we provide evidence for a neural dissociation between OCD and HCs in supporting abstract sequential behavior. We show that increased pACC and SFS/DLPFC ramping uniquely supports abstract sequencing in OCD compared to HCs and that anxiety and depressive

symptoms mediate the relationship between distinct neural activity and ER sequence and switch cost deficits in OCD. These results prompt future studies investigating the neural mechanisms of OCD to consider ramping as an important neural dynamic. Our work highlights specific cortical subregions within the broader CSTC framework that should be incorporated into models of OCD cognitive control dysfunction, with the potential to aid in refining future TMS treatment protocols to consider pACC/SFS targeting.

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