

Study Protocol and Statistical Analysis Plan (SAP)

Study Title: Improving Attentional and Cognitive Control in the Psychological Treatment of Intrusive Thoughts

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Notes: The detailed protocol describes both the pilot testing phase (Phase 1; n=3) and the randomized controlled trial phase (Phase 2; n=62). The data reported on ClinicalTrials.gov is only for the participants Phase 2.

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED RESEARCH PROTOCOL

Targeting Attentional and Cognitive Control to Enhance the Transdiagnostic Treatment of Repetitive Negative Thinking

1. BACKGROUND AND SIGNIFICANCE

Although cognitive behavioral therapy (CBT) is an efficacious first-line intervention for individuals with affective disorders, 40% of patients receiving CBT are deemed non-responders,^{1–3} possibly suggesting that underlying factors are not being fully addressed. Repetitive negative thinking (RNT) is a cognitive process central to the etiology and maintenance of many forms of psychopathology, including: *rumination* in major depressive disorder (MDD),⁴ *worry* in generalized anxiety disorder (GAD),⁵ and *mental rituals* in obsessive compulsive disorder (OCD).⁶ RNT predicts poor treatment outcome and is a common residual symptom following CBT.^{7–20} Thus, there is an urgent and unmet need to identify the mechanistic targets underlying RNT to optimize treatment response and reduce the psychiatric burden and healthcare costs for patients with affective disorders.

Given that a hallmark feature of RNT is difficulty controlling and disengaging from perseverative thoughts, recent theoretical models propose that deficits in attentional and cognitive control underlie RNT as fundamental biobehavioral targets.^{21–32} First, **attentional control**³³ includes the ability to: (a) *shift* attention away (i.e., disengage) from stimuli depending on task demands, and (b) *sustain* focus on goal-relevant information.^{34,35} Furthermore, **eye tracking** can delineate the components and time course of attentional processes.³⁶ Such measures harness gaze latency data (i.e., time to fixation) to distinguish between attentional engagement (i.e., shifting one's gaze from neutral to emotional stimuli when prompted) and attentional disengagement (i.e., shifting from emotional to neutral stimuli). Disorders characterized by elevated RNT appear to be specifically associated with difficulty disengaging from negative affective stimuli.^{37–42} Additionally, one's ability to sustain attention (i.e., maintaining focus once it has been established) in the face of distracting emotional stimuli may also become disrupted in affective disorders,^{43–45} but has been understudied in relation to RNT.

Second, these attentional difficulties can be activated in one of two contexts that rely on the dual mechanisms of **cognitive control**.⁴⁶ Cognitive control enables flexible allocation of mental resources (including attention) in the service of goal-directed behavior and is comprised of *proactive* (i.e., in preparation for a challenge) and *reactive* (i.e., in response to a challenge) contexts.^{47,48} Cognitive control capacity can be measured via **event related potentials (ERPs)**,⁴⁹ and ERP studies provide compelling evidence of altered cognitive processing in patients with depression, anxiety, and elevated RNT.^{43,50–54} Specifically, ERP cued task designs distinguish between (a) *proactive* and (b) *reactive* control. On the one hand, proactive control is initiated when a cue word indicates an upcoming conflict. Specifically, cue-locked **N2** ERPs in anticipation of conflict have been linked to detection of novel stimuli and orienting of attention,^{55–57} such that larger (more negative) amplitudes indicate the ability to allocate attentional/cognitive resources in proactive contexts. Reactive control, on the other hand, is initiated when responding to an emotional target stimulus. Specifically, target-locked **N2, N450, and P300** ERPs in response to conflict are linked to the adjusting of cognitive control processes,^{49,58,59} such that larger (more negative N2, N450; more positive P300) amplitudes indicate the ability to allocate

resources in reactive contexts. Yet, overall, studies validating these targets of attentional and cognitive control in treatment are lacking. Accordingly, the current study will address this need.

The Current Study

We will test the hypothesis that enhancing attention regulation skills in a transdiagnostic intervention streamlined and adapted for RNT – Attention Regulation – Emotion Regulation Therapy (AR-ERT)³¹ – will significantly improve the proposed target of attentional/cognitive control relative to a supportive psychotherapy (SPT) control group. Specifically, AR-ERT builds **attention regulation skills** (i.e., the ability to flexibly shift and sustain attention) to teach patients exercises for *Orienting* their attention and *Allowing* the presence of negative emotions. Patients are taught to apply these skills to counteract *reactive* perseverative thinking when negative emotions arise and to *proactively* engage with emotion-laden situations that trigger RNT.

The proposed project consists of two phases. In Phase I we will develop a streamlined version of ERT that is optimized to target attentional/cognitive control via attention regulation skills (AR-ERT).³¹ In Phase II we will test this intervention in a pilot randomized controlled trial using a sample of 62 patients with elevated RNT. Specifically, we will assess **target engagement** of attentional/cognitive control (i.e., sensitivity of our target to intervention-induced change) utilizing eye-tracking and ERP data. By enhancing attention regulation, we propose that AR-ERT will significantly improve the target of attentional/cognitive control for individuals with elevated RNT relative to those assigned to 8-weeks of SPT. Second, we will test preliminary **target validation**, and hypothesize that improvements in attentional/cognitive control will be associated with improved RNT and psychiatric functioning outcomes. If our hypotheses are supported, we will identify a transdiagnostic target that can be engaged to optimize treatment response for individuals with elevated RNT, enhancing the generalizability of our findings for maximum public health impact.

Innovation of the Proposed Study

The proposed study is highly innovative in several ways: (1) This is the first project to test a streamlined, mechanism-informed, transdiagnostic treatment for RNT.⁶⁰ (2) Our approach examines whether AR-ERT engages the target of attentional/cognitive control spanning multiple Research Domain Criteria (RDoC) units of analysis: behavioral (eye tracking fixations), electrophysiological (ERPs), self-report, and clinical interview. (3) In line with RDoC priorities, we will enroll individuals with elevated RNT, rather than those who meet diagnostic criteria for OCD, GAD, or MDD. This is important since RNT is a vulnerability factor for later psychopathology,^{4,61,62} and since we hope to examine future generalization to other conditions with RNT (e.g., post-traumatic stress disorder).

2. SPECIFIC AIMS

Primary Aim

Aim 1: Demonstrate target engagement with AR-ERT.

- **Hypothesis 1:** By enhancing attention regulation skills, AR-ERT will improve the biobehavioral target of attentional/cognitive control from pre- to post-treatment relative to a supportive psychotherapy (SPT) control group as measured by multi-method indices:
 - a) Behavioral: disengagement and sustained attention in the presence of emotional stimuli as measured by eye tracking fixations and reaction time,
 - b) Electrophysiological: proactive and reactive cue- and target-locked N2, N450, and P300 ERPs in a cued conflict monitoring task, and

- c) Self-report: perceived ability to shift and focus attention.

Secondary Aim

Aim 2: Assess if alteration in the hypothesized target is related to improvements in clinical outcomes (i.e., target validation).

- **Hypothesis 2a:** AR-ERT will improve RNT (transdiagnostic and disorder-specific measures) and psychiatric functioning (OCD, GAD, MDD symptoms; functional impairment) from pre- to post-treatment relative to SPT, with gains maintained at 3-month follow-up.
- **Hypothesis 2b:** Improvements in pre/post attentional/cognitive control will be associated with pre/post improvements in RNT and psychiatric functioning.

Exploratory Aim

We will use source localization to investigate neural generators of ERPs and resting state functional connectivity, with a focus on the default mode and frontoparietal networks.

3. SUBJECT SELECTION

A total of 3 pilot participants in Phase I and 62 participants in Phase II with elevated repetitive negative thinking (RNT) will participate in the proposed study. Participants will be selected based on the inclusion/exclusion criteria described below:

Inclusion criteria

- 1) Adults ages 18-60 years old
- 2) Right-handed, as assessed by the Edinburgh Handedness Inventory (score ≥ 61)
- 3) Living in Massachusetts
- 4) RNT in the form of mental rituals, worries, and/or depressive ruminations is the primary reason for seeking treatment (i.e., RNT is not better characterized by another disorder; e.g., post-traumatic stress disorder). Patients who present with multiple forms of RNT (e.g., mental rituals and worries), will be included to ensure generalizability and will be able to address each of these thinking patterns in treatment.
- 5) RNT severe enough to warrant intervention based on:
 - a. Moderate impairment on the Work and Social Adjustment Scale (WSAS total score ≥ 15 and ≥ 4 on any of the 5 sub-scales)
 - b. Score above the clinical mean on the Perseverative Thinking Questionnaire – Past Week (PTQ-PW ≥ 37)
- 6) Fluent in English, willing to provide informed consent, and willing to comply with the study protocol
- 7) Access to a device with an internet connection, camera, and microphone (e.g., computer, smart phone, tablet)
- 8) Comfortable and capable of using a computer and completing reaction-time tasks
- 9) Psychiatric comorbidities not listed in exclusion criteria below will be allowed

Exclusion criteria

1. History of head injury resulting in prolonged loss of consciousness and/or neurological sequelae; History of seizures; History of stroke; Signs of increased intracranial pressure; Prior neurosurgical procedure
2. Current or history of neurologic or psychiatric disease (e.g., dementia, brain damage, or other cognitive impairment), mental retardation, or borderline intellectual functioning that would interfere with ability to participate in the study

3. Impaired (or uncorrected) vision, medical illness, or medical treatment that would likely interfere with participation
4. Active suicidal or homicidal ideation, as assessed by the Structured Clinical Interview for DSM-5-Research Version (SCID-5-RV), Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D), and/or score on the Beck Depression Inventory (BDI-II) suicide item (#9) ≥ 2 , or any features requiring a higher level of care
5. Lifetime psychotic disorder or bipolar disorder; as determined by SCID-5-RV
6. Moderate substance or alcohol use disorder within the past 3 months that would interfere with treatment; as determined by SCID-5-RV
7. Current Attention Deficit Hyperactivity Disorder (ADHD) that would complicate interpretation of performance on the attentional/cognitive target measures; as determined by SCID-5-RV
8. Unstable dose of psychotropic medications (i.e., dose changes within 2 months of study baseline) or discontinuation of psychotropic medication less than 2 months prior to study baseline. Plans to initiate psychotropic medication or change dose during the study. Patients can be receiving psychotropic medication if they have taken a stable dose for at least two months before the study baseline assessment and the dose remains stable during the study to maximize generalizability of the sample.
9. Current psychotherapy or plans to initiate such treatment during the study.
10. Previous treatment with ≥ 4 sessions of cognitive behavioral therapy and/or mindfulness/meditation for obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), or depression

Recruitment

The study will recruit subjects who meet the above inclusion/exclusion criteria using approaches that are standard for clinical research studies and that the Massachusetts General Hospital (MGH) Center for OCD and Related Disorders has used successfully in previous clinical trials. Specifically, participants will be recruited via advertisement, clinician referral, and self-referral to the Center for OCD and Related Disorders. Our program is one of the largest in the world that treats individuals with OCD. In order to further strengthen feasibility, subjects with worries will be referred from the MGH Center for Anxiety and Traumatic Stress Disorders (CATSD) Program and subjects with depressive ruminations will be referred from the MGH Depression Clinical and Research Program (DCRP).

Participants will also be recruited from the greater community to strengthen recruitment and diversify the sample. Specifically, we will advertise on the MGH Center for OCD and Related Disorders website and on other websites (e.g., Rally, the International Obsessive Compulsive Disorder Foundation). We will use the RSVP for Health and Research Match websites to identify potentially eligible individuals with OCD, GAD, or MDD. We will post flyers at MGH, in the Boston area, and surrounding towns. Our lab also advertises for our program more broadly in local media outlets (e.g., newspaper), the Boston subway, and buses (through the General Recruitment Protocol # 2009P002227). Our recruitment methods have been used successfully in previous studies, and we do not anticipate any difficulties obtaining the proposed sample. Our recruitment strategies also follow the guidelines on the National Institute of Health (NIH) website to ensure racial/ethnic diversity, and many of our recruitment strategies (e.g., newspaper advertisements) specifically will focus on minority groups.

4. SUBJECT ENROLLMENT

Pre-Screening Phase

Our program has a pre-screening procedure that we will follow. First, interested participants will be directed to an online pre-screen electronically via REDCap™ which will include the Perseverative Thinking Questionnaire – Past Week (PTQ-PW) and the Work and Social Adjustment Scale (WSAS). Participants with scores indicating at least moderate levels of RNT (PTQ-PW ≥ 37 ; WSAS total score ≥ 15 and ≥ 4 on any of the 5 sub-scales) will be contacted by a highly trained research assistant to schedule a phone screening. This screening will include questions to assess for RNT symptoms (mental rituals, worries, ruminations) and determine whether study inclusion/exclusion criteria appear to be met. Those with who appear to meet study inclusion/exclusion criteria and who are interested in participating will be given information about the study. For potential subjects who are receiving psychotropic medication and/or concurrent therapy and wish to participate in our study (and we agree that this is a reasonable option), we may obtain their consent to contact their treating clinician to determine the appropriateness of study participation. Callers who do not meet study entry criteria or do not wish to participate will be referred for treatment in our program or elsewhere. We will track the number of screens, number of eligible subjects, and reasons for nonparticipation. We will have weekly meetings to discuss individuals who contact our program and their appropriate disposition.

Email Policy. All emails sent to participants (e.g., to remind participants about study assessments, to provide participants with links to the REDCap surveys) will be sent from the study staff's Partners/MGH email account, via "Send Secure" encrypted email or without Send Secure in cases where participants have opted out of Send Secure emails via the following Partners Privacy Office procedures: "Before sending or responding to an unencrypted email message to an individual, the individual must acknowledge understanding of, and agreement to accept the risks as communicated to them via the following language (this language must be copied into an email response to an individual, or may be read over the phone to the individual, or an individual could agree by reading this in person and signing this or simply agreeing verbally):"

Opt out language: "The Partners standard is to send email securely. This requires you to initially set up and activate an account with a password. You can then use the password to access secure emails sent to you from Partners HealthCare. If you prefer, we can send you "unencrypted" email that is not secure and could result in the unauthorized use or disclosure of your information. If you want to receive communications by unencrypted email despite these risks, Partners HealthCare will not be held responsible. Your preference to receive unencrypted email will apply to emails sent from this research group/study only."

If a participant opts out of Send Secure emails, this decision (and the opt out date) will be documented in the participant's research record.

Screening Phase

Individuals who appear eligible for and are interested in the study during the phone screen will then be scheduled for a screening assessment with the PI (Dr. Jacoby). The screening assessment will take place virtually using Healthcare Secure Zoom™ or over the phone (if this method is preferred by the participant). The PI (or doctoral-level delegate) will obtain informed consent using the e-consent module in REDCap™, conduct a diagnostic clinical interview, and subjects will complete online self-report questionnaires (see Table 1 below for more detail). Finally, eligibility for the study will be confirmed by the PI. When interviewed patients do not qualify for or choose not to participate in the study, reasons will be documented. Altogether, the screening procedures will take an estimated 2.5 hours.

5. STUDY PROCEDURES

Overview

This is a single-site study at the MGH Richard B. Simches Research Center (Boston, MA) and Athinoula A. Martinos Center for Biomedical Imaging (Charlestown, MA). Eligible participants will complete: (1) 3 electroencephalogram (EEG) sessions which record brain activity while participants sit at rest (i.e., resting state functional connectivity) and perform a computer task (2 hours), (2) 3 computer task sessions in which participants view a series of images (i.e., faces, scenes), and we measure where on the screen they are looking using an eye tracker and the sweatiness of their palms (60-90 min), (3) an 8-week therapy protocol (60 minutes each) – with random assignment to either Attention Regulation – Emotion Regulation Therapy (AR-ERT) or supportive psychotherapy (SPT), and (4) 4 clinical assessment visits including clinician interviews and self-report measures at baseline (week 0), mid-treatment (week 4), post-treatment visit (week 8), and 3-month follow-up (week 20). The EEG sessions will take place at the Martinos Center and the computer task sessions will take place at the MGH Center for OCD and Related Disorders in Simches. Clinical assessments will take place virtually using Healthcare Secure Zoom™, an encrypted and HIPAA-compliant video conferencing platform (or over the phone). Treatment visits will also take place virtually and will be conducted using Healthcare Secure Zoom™ (or over the phone). Twenty-four hours prior to EEG and computer task sessions, participants will be screened for COVID-19 symptoms by completing the MGB COVID-19 Prescreen Questions. Subjects will be given the option of combining the screening and baseline clinical assessment visits (if they are deemed eligible for the study after screening) and combining the mid-treatment and post-treatment clinical assessment visits to their treatment session visits (to reduce subject burden). Thus, study participation may only involve 16 total visits if such visits are combined. To avoid dropout, subjects will be paid \$20 each for the baseline, mid-treatment, post-treatment, and 3-month follow-up clinical assessments, \$20 each for the 3 EEG sessions, and \$20 each for the 3 computer task visits (\$200 total). Participants who cannot afford to travel to the treatment facility will be provided with transportation fare (e.g., parking passes) to attend in-person study visits (\$12.50 x 3 computer task visits at the Simches Building + \$7 x 3 EEG sessions at the Martinos Center = \$58.50).

If an enrolled participant has already completed the same clinician-administered within the past six months as part of a different study within the Center for OCD and Related Disorders, CATSD, or DCRP Programs, we may offer them the opportunity to consent to give us permission to access data from their previous screening assessment.

Clinical Assessments

Table 1 below shows the assessment schedule. Most measures are administered at baseline (week 0), midpoint (week 4), post-treatment (week 8), and 3-month follow-up (week 20); each 1-1.5 hours. Additionally, certain measures will be administered weekly at therapy visits (10 minutes). These times are comparable to those in the clinic's other treatment studies and have been well tolerated. All assessments are non-invasive and demonstrate good psychometric properties (e.g., internal consistency, construct validity). No data will be gathered from outside sources (e.g., medical records). To facilitate completion of assessments and increase quality of data, most assessments will be completed electronically via the online data collection site REDCap™ (described further in "Data Management" below).

Diagnostic and Screening Measures

Structured Clinical Interview for DSM-5 Disorders - Research Version (SCID-5-RV)⁶³: The SCID-5-RV is a reliable semi-structured instrument that is the standard in the field for diagnosing current and lifetime psychiatric disorders. The SCID-5-RV also includes a section for collecting demographic and historical data including information about lifetime suicidal ideation and behavior and psychiatric hospitalizations. The SCID-5-RV will be administered by the PI at the screening visit (using the online NetSCID) in order to characterize the sample and determine the presence of any exclusionary diagnoses.

Test of Premorbid Functioning (TOPF)⁶⁴: In order to screen for intellectual impairment, the TOPF will be administered at the baseline visit to estimate cognitive and memory functioning.

Table 1: Assessment Measures by Study Visits

Measure Type	Measure	Admin by	Week -1 (Screen)	Week 0 (Baseline)	Week 4 (Mid-Tx)	Week 8 (Post-Tx)	Week 20 (3MFU)
Diagnosis & Screening	SCID-5-RV	PI	X				
	TOPF	RA		X			
	Medical and Treatment History Logs	PI	X				
	Demographics	Self	X				
	EHI	PI	X				
Target (Cognitive/ Attentional Control)	ACS	Self		X	Weekly	X	X
	AEDT	RA		X	X	X	
	EIT	RA		X	X	X	
	CECT	RA		X	X	X	
Outcome (RNT)	PTQ-PW	Self	X	X*	Weekly	X	X
	PSWQ	Self		X	X	X	X
	RRS	Self		X	X	X	X
	ROCS	Self		X	X	X	X
Symptoms	Y-BOCS	IE		X	X	X	X
	SIGH-A	IE		X	X	X	X
	SIGH-D	IE		X	X	X	X
	DOCS	Self		X	X	X	X
	STAI-T	Self		X	X	X	X
	BDI-II	Self		X	X	X	X
	CGI-S/I: Clinician	IE		X	X	X	X
	CGI-I: Patient	Self			Weekly	X	X
Functioning	WSAS	Self	X	X*	X	X	X
	Q-LES-Q-SF	Self		X	X	X	X
Safety	BDI-II Suicide Item (#9)	Self	X		Weekly		
	CMED Log	RA/Ther		X	Weekly	X	X
	CTHER Log	RA/Ther		X	Weekly	X	X
	Life Events Questionnaire	RA/IE		X	X	X	X
	AE Form / AE Log	RA/Ther		X	Weekly	X	X
Tx Details	CEQ	Self		X	Session 8		
	CSQ-8	Self				X	
	WAI-SR	Self/Ther			X		
	Homework Compliance	Self/Ther			Weekly		
	Adherence/Competence	IRR			Weekly		
	Blinding Questionnaire	Ther					X

Measure Type	Measure	Admin by	Week -1 (Screen)	Week 0 (Baseline)	Week 4 (Mid-Tx)	Week 8 (Post-Tx)	Week 20 (3MFU)
Other	Lifetime Medication History	Self		X			
	IUS-12	Self		X	X	X	X
	Health Behaviors Questionnaire	RA		X	X	X	
	Post-EEG Questionnaire	Self		X	X	X	
	COVID-19 Impact Scale	Self		X	X	X	X
	eACS	Self		X	X	X	X
	EQ-D	Self		X	X	X	X
	ERQ	Self		X	X	X	X
	Treatment Preference Form	Self	X				
	Patient Feedback Questionnaire	Self				X	
	After ART Usage and Additional Tx Form	Self					X

*PTQ-PW and WSAS to be repeated at baseline if it has been >7 days since screening visit

Medical and Treatment History Logs: This measure will be administered by the PI at the screening visit to assess for: (a) lifetime medical problems that are exclusionary in this study, and (b) treatment history with psychotropic medications within the last 2 months and lifetime psychosocial treatments to assess for current/lifetime treatment exclusions.

Participants will also complete a **Demographics** self-report form to characterize the sample (e.g., gender, race, education, occupational status) and the **Edinburgh-Handedness Inventory (EHI)**⁶⁵ rated by the PI to confirm handedness at the screening visit.

Target Measures of Attentional/Cognitive Control

Attentional Control Scale (ACS)³³: The ACS a 20-item self-report instrument in the NIH Toolbox⁶⁶ that measures participants' perceived ability to (a) focus on relevant stimuli while ignoring distractors (e.g., "My concentration is good even if there is music in the room around me"), and (b) shift attention (e.g., "After being interrupted or distracted, I can easily shift my attention back to what I was doing before"). The ACS will be administered at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) as well as weekly during the therapy visits.

Attentional Engagement-Disengagement Task (AEDT)⁴⁰: The AEDT will be used as a behavioral measure of attentional control. Two emotional faces are presented (happy, disgusted, and sad paired with neutral faces; Radboud Faces database)⁶⁷ and eye tracking is measured; 72 trials. Half of trials measure (a) *attentional engagement* with emotional expressions (i.e., once participants fixate on the neutral face, a frame around the emotional face indicates they should shift their gaze), and the other half measure (b) *attentional disengagement* (i.e., shifting from emotional to neutral). Gaze latency (i.e., time to fixation) is the main outcome. This task has been linked to rumination⁶⁸ and is sensitive to treatment.⁶⁹ It is expected that individuals with RNT will display delayed disengagement (i.e., longer time to fixation) when shifting from negative to neutral stimuli (vs. from positive to neutral or from neutral to emotional)³⁷⁻³⁹, which is expected to improve with ERT-AR. Eye movements will be recorded using a Tobii Pro X3-120 (described in "Equipment" below). The AEDT will be administered at the following timepoints: baseline (week 0), mid-treatment (week 4), and post-treatment (week 8). Computer task sessions will occur within a 7-10-day window, but no longer than 14 days from each clinical assessment visit.

Emotional Interference Task (EIT)⁷⁰: The EIT measures difficulties *sustaining attention* in the presence of distressing emotional contexts. Participants view 40 neutral and 40 arousing (20 pleasant and 20 unpleasant) photographs from the International Affective Picture System (IAPS)⁷¹ for 6 seconds each, in random order, with a 1-second interval between pictures (148 trials). A high- or low-pitched tone is played either 1 or 4 seconds after each picture is presented, and participants are instructed to choose whether each tone is high or low by pressing a button as quickly as possible after each tone is played. Mean reaction times are calculated separately for pleasant, unpleasant, and neutral pictures. Emotional interference is then calculated separately for pleasant and unpleasant stimuli by subtracting mean reaction times recorded while viewing neutral pictures from mean reaction times recorded while viewing pleasant and unpleasant pictures. Faster reaction times reflect better ability to inhibit emotional interference while sustaining attention on the tone; we will also collect gaze data to validate for future research. Past research has indicated that patients with GAD demonstrate slower reaction times on the EIT vs. controls, and symptom improvement is associated with faster reaction times.^{43,72} The EIT will be administered at the following timepoints: baseline (week 0), mid-treatment (week 4), and post-treatment (week 8). Computer task sessions will occur within a 7-10-day window, but no longer than 14 days, from each clinical assessment visit.

Psychophysiological Measurement. Galvanic Skin Response (GSR) will also be measured during the EIT at baseline, mid-treatment, and post-treatment. Biometric measurement of this psychophysiological index will be recorded using the iMotions platform.

Cued Emotional Control Task (CECT)⁷³: The CECT is an electrophysiological measure of cognitive control based on well-validated cognitive conflict paradigms (i.e., emotional Stroop,⁷⁴ Etkin Conflict Adaptation Task⁷⁵). Each of the 216 trials begins with one of three 500ms word cues: “actual” to press a key to indicate the emotional expression of the upcoming target face (e.g., press “sad” to sad face); “opposite,” to indicate the emotion opposite the one expressed (e.g., press “happy” to sad face); or “press”, to press a key regardless of the expression. Targets are happy or sad emotional faces (500 ms; Karolinska Directed Emotional Faces dataset, KDEF).⁷⁶ This allows for measurement of cued preparatory processes in *anticipating* an emotional stimulus (i.e., proactive control) vs. reactive control in *responding* to one, using cue- and target-locked ERPs, respectively. The difference in responding on high conflict (“opposite”) vs. low conflict (“actual”) trials isolates the process of cognitive control. Outcomes include the N2, N450, and P300 ERP amplitudes. Research with high trait ruminators demonstrates this task is associated with rumination⁵⁴ and is sensitive to treatment.⁷⁷ Individuals with RNT are expected to display reduced cue- and target-locked ERPs with negative faces, and improvement following AR-ERT would be indicated by less cognitive cost between low vs. high conflict trials. EEG data will be collected with a 96-channel EEG cap (BrainVision, LLC; described in “Equipment” below). Data from the CECT will be averaged to form the ERPs of interest.

Source localization will rely on standardized Low Resolution Electromagnetic Tomography (sLORETA)^{78,79} to identify neural generators of each ERP component.^{79,80} We also will collect 8-minutes of resting (task-free) EEG data, and exact LORETA (eLORETA) will be used to analyze **resting state functional connectivity**.⁸¹

The CECT and resting state functional connectivity will be collected at the following timepoints: baseline (week 0), mid-treatment (week 4), and post-treatment (week 8). EEG sessions will occur within a 7-10-day window, but no longer than 14 days, from each clinical assessment visit.

Outcome Measures of Repetitive Negative Thinking (RNT)

Perseverative Thinking Questionnaire – Past Week (PTQ-PW)⁸²: The PTQ-PW is a 15-item self-report measure of transdiagnostic repetitive negative thinking within the past week. Items on the PTQ-PW are independent of disorder-specific content and inquire about thoughts as repetitive, intrusive, unproductive, and capturing mental capacity (e.g., “The same thoughts keep going through my mind again and again”). The PTQ-PW is our primary outcome measure. It will be administered at the screening visit to determine eligibility (PTQ-PW \geq 37), the assessment visits (baseline *if more than 7 days has passed since screening*, mid-treatment, post-treatment, and 3-month follow-up), and weekly during the therapy visits.

Disorder-specific presentations of RNT will additionally be captured via the following measures, which will each be collected at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up):

Penn State Worry Questionnaire (PSWQ)⁸³: The PSWQ is a 16-item self-report scale that measures the tendency to engage in excessive, uncontrollable, generalized worry (e.g., “I am always worrying about something”).

Rumination Response Scale (RRS)⁸⁴: The RRS is a 22-item self-report questionnaire that measures participant general responses to sad or depressed mood (e.g., “think about how sad you feel.”).

Rumination on Obsessions and Compulsions Scale (ROCS)⁸⁵: The ROCS is a 33-item self-report measure that assesses the frequency of various responses (e.g., “I distract myself with anything that comes to mind”) to intrusive thoughts or images in the past month.

Symptom Measures

The following gold-standard interview measures will be administered by the IE at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) to assess OCD, GAD, and depression symptom severity respectively:

Yale-Brown Obsessive Compulsive Scale (Y-BOCS)^{86,87}: This 12-item rater-administered semi-structured scale includes a checklist of common obsessions and compulsions and rates severity (distress and impairment) of OCD symptoms over the past week.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A)⁸⁸: The SIGH-A is a 19-item structured, clinician-administered rating scale that provides an overall measure of generalized anxiety in the past week.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D)⁸⁹: The SIGH-D is a 17-item clinician-administered measure of overall severity of depressive symptoms in the past week.

The following self-report measures will also be administered at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) to assess OCD, GAD, and depression symptom severity respectively:

Dimensional Obsessive-Compulsive Scale (DOCS)⁹⁰: The DOCS assesses the symptom severity of the following four OCD symptom dimensions: (a) concerns about germs and

contamination, (b) responsibility for harm, injury, or bad luck, (c) unacceptable thoughts, and (d) concerns about symmetry, completeness and need for things to be “just right”.

State Trait Anxiety Inventory-Trait (STAI-T)⁹¹: The STAI-T is a 20-item questionnaire of trait anxiety in which respondents are asked to rate the intensity of their feelings in general (e.g., “I am tense”).

Beck Depression Inventory (BDI-II)⁹²: This 21-item self-report inventory is a widely used measure of depression severity that assesses the affective, cognitive, motivational, vegetative, and psychomotor components of depression.

Clinical Global Impression Scale – Severity and Impairment (CGI-S/I)⁹³: The CGI-Severity (CGI-S) is a measure of the global severity of symptoms. It ranges from 1 (normal, not ill at all) to 7 (among the most extremely ill patients) and is commonly used in clinical trials. The CGI-S will be administered by the IE at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up).

The CGI-Improvement (CGI-I) is a global rating scale of improvement during treatment that ranges from 1 (very much improved) to 7 (very much worse). Subjects will complete a CGI-I for RNT symptoms (CGI-RNT) and for overall anxiety, mood, and mental health symptoms (CGI-Global) at each therapy visit, at mid-treatment, post-treatment, and at 3-month follow-up. The IE will complete the CGI-RNT and CGI-Global at the following assessment visits: mid-treatment, post-treatment, and 3-month follow-up. The CGI-I will be used to determine whether subjects experience clinical deterioration and should be withdrawn from the study (see section on “Participant Withdrawal” below).

Functioning and Quality of Life

Work and Social Adjustment Scale (WSAS)⁹⁴ The WSAS is a 5-item self-report scale assessing disability in work, home management, social leisure activities, private leisure activities, and the ability to form and maintain close relationships, each on 8-point scales. A composite score can be calculated by summing the five scales for a dimensional measure of global functional impairment that ranges from 0 to 40, in which higher scores denote greater disability. Specifically, WSAS total scores less than 15 indicate mild disability, between 15 and 30 moderate disability, and greater than 30 severe disability. The WSAS will be administered at screening to determine eligibility (moderate impairment of RNT; WSAS total score ≥ 15 and ≥ 4 on any of the 5 sub-scales) and at the clinical assessment visits (baseline *if more than 7 days has passed since screening*, mid-treatment, post-treatment, and 3-month follow-up).

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)⁹⁵: The Q-LES-Q-SF is a 16-item self-report measure of quality of life, often used in treatment studies, that focuses on social relationships, emotional well-being, physical health, leisure activities, work, school, and household duties. The Q-LES-Q-SF will be administered at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up).

Assessment of Safety, Concomitant Treatment, and Adverse Events

Beck Depression Inventory (BDI-II) – Suicide Item⁹²: Item #9 of the BDI-II regarding suicidal thoughts or wishes will be given at screening to determine eligibility (scores ≥ 2 are exclusionary, “2 - I would like to kill myself” and “3 - I would kill myself if I had the chance”). This item also will be administered weekly to monitor suicidal ideation.

Concomitant Medication (CMED) Log: The RA will administer the CMED form at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) and before each therapy session to probe for any changes in medications for mood, anxiety, sleep, or other psychological symptoms that may have occurred since the last session. Changes in psychotropic medications or dose are not allowed during the study. At each visit, the research coordinator will update the CMED Log to track all psychotropic medications, including dose. The therapist will review the completed CMED Log before each therapy session.

Concomitant Therapy (CTHER) Log: The RA will administer the CHER form at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) and before each therapy session to probe for any changes in therapy that may have occurred since the last session. Changes in therapy are not allowed during the study. At each visit, the research coordinator will ask the subject whether they have started or stopped any mental health treatments such as counseling, therapy, or self-help programs to ensure that this does not occur without our knowledge. The therapist reviews the completed CHER Log before each therapy session.

Life Events Questionnaire: This form is administered by the RA and reviewed by the PI at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) to assess whether any major life events occurred since the last assessment visit that might have had a psychological impact on the participant including: marriage, divorce or separation from spouse, death of a spouse/partner or other close family member, birth of a child, serious injury, diagnosis/progression of a medical illness or disease (e.g., COVID-19 exposure or diagnosis), loss/began new job.

Adverse Events (AE) Form and Log: The AE Form will be administered by the RA during clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) and by the therapist during treatment sessions to probe for any adverse events. Should the participant report an adverse event, the RA or therapist will log this information in the AE log while speaking to the participant. If there are any safety concerns during a clinical assessment, the RA will inform the IE of the adverse event. The RA and therapist will document any adverse events that occur during the study and the PI will review each event during weekly study meetings to discuss relatedness to treatment, severity, and corrective actions. We have used these forms in prior NIH-funded psychotherapy studies.

Assessment of Treatment Credibility and Satisfaction:

Credibility/Expectancy Questionnaire (CEQ)⁹⁶: This 6-item self-report questionnaire has two subscales: (1) treatment rationale credibility (CEQ-C) is cognitively based (e.g., “How logical does the therapy offered to you seem?”), and (2) treatment expectancy (CEQ-E) is emotionally based (e.g., “How much do you really feel that therapy will help you to reduce your symptoms?”). The CEQ will be administered at the baseline clinical assessment visit (week 0) as well as at the start of session 3.

Client Satisfaction Questionnaire (CSQ-8)^{97,98}: This 8-item self-report questionnaire assesses satisfaction with clinical services received. The CSQ will be administered at the post-treatment clinical assessment visit (week 8).

Working Alliance Inventory (WAI-SR)⁹⁹: The WAI-SR is based on Bordin’s (1979) conceptualization of therapeutic alliance¹⁰⁰ which includes three factors: (1) bond alliance (e.g.,

“___ and I respect each other”), (2) goal alliance (e.g., “___ and I are working towards mutually agreed upon goals”), and (3) task alliance (e.g., “___ and I agree on what is important for me to work on”). Compared to the original 36-item WAI, the revised short version (WAI-SR) has an improved model fit in confirmatory factor analyses¹⁰¹.

Homework Compliance: Therapists and patients are asked to rate the amount of between-session homework participants completed on a scale from 1 (patient did not attempt the assigned homework) to 5 (patient did more of the assigned homework or its equivalent than was requested). Therapists and patients also rate effort made by the patient in completing the assignment on a scale from 0 (patient made no attempt to complete any homework) to 4 (patient made maximal efforts to complete homework). Finally, therapists rate the relevance of the homework attempted to the patient’s particular problem on a scale from 0 (homework attempted was completely unrelated or not done) to 4 (homework attempted relevant to particular target problems). These measures have been used in previous studies of ERT³¹ and will be administered weekly at the therapy sessions.

Adherence and Competence^{31,102}: For supportive psychotherapy, manual adherence on a scale from 1 (not at all) to 7 (completely) and competent treatment delivery on a scale from 1 (not at all) to 5 (completely) will be rated to ensure minimum scores of ≥ 6 on adherence and ≥ 4 on competence for selected sessions (as described below under “Monitoring and Quality Assurance”). For attention regulation therapy, manual adherence will be rated on a scale from 0 (did not address component/engage action) to 2 (addressed component/engaged action in more detail), and competent treatment delivery will be rated on a scale from 0 (therapist was not skillful or performed poorly) to 2 (therapist performed action very skillfully). The specific skills to be rated on this measure were developed during the study and submitted as an IRB amendment.

Blinding Questionnaire: This measure will be completed by the IE at 3-month follow-up in order to assess whether they believe the participant has been assigned to AR-ERT or SPT and how strongly they believe this (i.e., somewhat or strongly).

Other Assessments

The **Lifetime Medication History** self-report form reviews lifetime medication treatment (i.e., prior to past 2 months).

Intolerance of Uncertainty Scale (IUS-12)¹⁰³: The IUS-12 is a self-report measure capturing reactions to uncertainty, ambiguity, and the future and consists of two subscales: (a) *Prospective IU* measures discomfort due to future unknowns and information gathering to increase certainty (e.g., “I always want to know what the future has in store for me”), and (b) *Inhibitory IU* measures avoidance and paralysis in the face of uncertainty (e.g., “When I am uncertain I can’t function very well”). The IUS-12 will be administered at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up).

Health Behaviors Questionnaire: This measure will be administered at the computer task visits (baseline, mid-treatment, post-treatment) in order to assess health-related behaviors participants may have engaged in over the past 24 hours that would affect interpretation of the physiological readings.

Post-EEG Questionnaire: This questionnaire probes whether participants were uncomfortable, anxious, sleepy, or inattentive during the EEG recording and will be administered directly after each EEG session (baseline, mid-treatment, post-treatment).

COVID-19 Impact Scale: This 14-item self-report measure was created by members of the Center for OCD and Related Disorders and aims to assess the effect of the coronavirus pandemic on individuals in the past week. Individuals are instructed to rate the extent to which they agree/disagree with various statements (e.g., “I found it difficult to tolerate the uncertainty about whether I or a loved one would contract COVID-19”) on a scale from 1 (Strongly Disagree) to 5 (Strongly Agree). The COVID-19 Impact Scale will be administered at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up).

Experiences Questionnaire - Decentering (EQ-D)¹⁰⁴: In this 11-item subscale, individuals are asked to indicate how often they currently have various decentering experiences (e.g., “I am consciously aware of a sense of my body as a whole”) on a scale from 1 (Never) to 5 (All the time). The EQ-D will be administered at baseline, mid-treatment, post-treatment, and 3-month follow-up.

Emotion Regulation Questionnaire (ERQ)¹⁰⁵: The ERQ is a 10-item self-report measure of emotion regulation that includes statements related to *cognitive reappraisal* (e.g., “When I’m faced with a stressful situation, I make myself *think about it* in a way that helps me stay calm”) as well as *expressive suppression* (e.g., “I control my emotions by *not expressing them*”). Individuals are asked to rate the extent to which they disagree/agree with these statements on a scale from 1 (Strongly disagree) to 7 (Strongly agree). The ERQ will be administered at baseline, mid-treatment, post-treatment, and 3-month follow-up.

Emotional Attentional Control Scale (eACS)¹⁰⁶: This 14-item self-report measure, which was adapted from the original 20-item Attentional Control Scale (ACS), assesses modulation of attentional control in emotional contexts. Individuals rate each item on a 4-point scale from 0 (almost never) to 4 (always). The eACS will be administered at baseline, mid-treatment, post-treatment, and 3-month follow-up.

Treatment Preference Form: This self-report form aims to capture the degree to which each participant prefers a given treatment condition (AR-ERT or SPT) before they are randomized. Participants are made aware that this form will have no bearing on treatment assignment and will not be viewed until after the participant has completed treatment.

Patient Feedback Questionnaire: This questionnaire allows participants to provide feedback on their experience during treatment, including general satisfaction with their treatment condition and treatment length, which aspects of therapy they found most confusing or most helpful, and usefulness of the therapy website and forms. This self-report questionnaire will be administered at post-treatment only.

After ART Usage and Additional Treatment Form: This self-report form asks participants to report their usage and the usefulness of the study website, and probes for the need for additional treatment at the 3-month follow up assessment.

Equipment

Eye-tracking data will be collected during the AEDT and EIT tasks. The eye tracking equipment will be located in a dedicated office within the OCD Program. We will use a Tobii Pro X3-120 screen-based eye tracker (The Tobii Group, Danderyd, Sweden) which samples eye-

gaze coordinates at 120 Hz. Eye tracking data will be transmitted via USB 3.0 to a LAN with External Processing Unit and converted to visual fixation data using the iMotions Biometric Research Platform (Boston, MA, USA).

The electroencephalogram (EEG) equipment is located at the MGH Martinos Center (Charlestown, MA). EEG data will be acquired using BrainVision software (Brain Products GmbH, Gilching, Germany) that is installed in a dedicated behavioral testing laboratory. The EEG amplifier is an actiCHamp active amplification system (24-bit battery, up to 1000 Hz sampling rate). It is used with actiCAP EEG caps, which are fitted with 32-electrode modules. Our system is configured for use with 96 electrodes (3 modules) to provide dense scalp coverage, which is helpful for spatially localizing event related potentials (ERPs) and is necessary for accurate source localization. The cap can be fit to a participant in about 30 minutes to provide an individualized and comfortable fit for each person. The actiCHamp system uses active electrodes and gel to minimize impedance and maximize signal-to-noise ratio (SNR); impedances will be kept under 30 kOhms to ensure high SNR. The N2 and N450 ERP components will be measured at midline frontal (Fz) and central (Cz) sites, while the P300 will be measured at a midline parietal site (Pz). Digitization of three-dimensional electrode positions will be accomplished via the BrainVision CapTrak system. Data processing and analysis will occur offline using BrainVision Analyzer 2.0 and MatLab (Natick, MA, USA).

Randomization

At the baseline visit, eligible subjects will be randomized (1:1 in parallel) to AR-ERT or SPT using the REDCapTM database.

Treatment

For all participants, treatment will consist of 8 weekly sessions provided via Healthcare Secure ZoomTM that are 60 minutes in duration. Eight sessions is the length of ERT currently being tested,^{107,108} allowing us to directly compare our effect sizes with the full package. All sessions are individual treatment (no group treatment).

Attention Regulation – Emotion Regulation Therapy (AR-ERT)

A brief, manualized version of individual Emotion Regulation Therapy (ERT) focused on the Attention Regulation module will be administered to patients randomized to AR-ERT. Specifically, the 8-session protocol will be a streamlined version of ERT, which tested as part of a NIH-sponsored R34:MH070682. The full protocol^a engages several active mechanisms (i.e., attention regulation, metacognitive regulation, reward/threat processing) and an 8-session version of this full treatment is currently being studied; however, in order to test the target of attentional/cognitive control, we are focusing solely on attention regulation skills: (a) Orienting (i.e., the ability to flexibly shift attention) via mindfulness of the breath (sessions 1-4), and (b) Allowing (i.e., the ability to sustain attention despite unpleasant emotional experiences) via mindfulness of thoughts and emotions (sessions 5-8). Treatment will also include lessons for practicing these skills in two different contexts: (a) reactive: reviewing challenging (i.e., emotion-laden) situations that have happened in the past week in which attention regulation skills could have been applied to counter automatic reactive RNT responses (sessions 1-4) as well as (b) proactive: preparing for challenging situations that may happen in the future in which skills could be implemented (sessions 5-8).

Specifically, session 1 provides patients with a model of how RNT maintains emotions, presents between-session self-monitoring of RNT, and introduces the attention regulation skill of Orienting via mindfulness of the breath. In sessions 2-4, Orienting skills continue to be practiced. Patients review their self-monitoring forms to detect triggers and consequences of RNT. They also conduct in-session imaginal rehearsal of situations from the past week that

didn't go as planned in order to explore effective alternatives (i.e., earlier cue detection of RNT; how attention regulation skills could have been applied to counteract RNT). Session 5 begins the second half of treatment, in which the skill of Allowing is introduced via mindfulness of thoughts and emotions. In addition, proactive strategies are taught to prepare for emotion-laden situations that trigger RNT that patients may be avoiding, have withdrawn from, or that RNT prevents them from fully experiencing. Specifically, session 5 includes in-session imaginal rehearsal of upcoming situations that the patient wants to engage in, including confronting imagined difficulties and feared outcomes. In sessions 6-7, Allowing will continue to be practiced. Proactive imagery exercises also continue and additionally involve *in vivo* proactive exercises to approach situations that typically trigger RNT. Finally, session 8 includes a summary of patients' gains, relapse prevention, and processing of termination. Home practice assignments are assigned after each session. Materials needed to complete between-session assignments will be emailed to participants using REDCap as well as housed on a website (<https://mghocd.org/art/>). This website will not store any data; instead, it will simply host links to various materials (e.g., links to PDFs for them to download, links to pre-recorded session recap videos summarizing the skills associated with that session, and links to REDCap surveys). The website (hosted by Wordpress) will require a passcode to enter ("attention"), which will only be shared with participants receiving Attention Regulation - Emotion Regulation Therapy.

Supportive Psychotherapy (SPT)

To control for nonspecific therapy elements (e.g., expectancies, demand characteristics), half of participants will be randomized to SPT.^{109–113} SPT is one of the most common psychological therapies provided in the community for affective disorders,¹¹⁴ and thus is a credible control condition (which will minimize attrition), yet it is not hypothesized to engage the target of attentional/cognitive control. SPT is also acceptable from a safety perspective, as it allows close patient monitoring. Manualized SPT has been used as the control condition in other NIH-funded studies in our program.

SPT focuses on therapeutic interactions and techniques that are nonspecific and common to psychotherapies (e.g., reflective listening, expression of empathy), and sessions are non-directive and conversational, with content driven by the patient.¹¹⁵ SPT focuses on maintaining, improving, and restoring self-esteem and adaptive coping skills, and on reflecting and expressing emotions about current life issues. The intent is to help patients learn to cope with external and internal (psychological) challenges.^{115–117} SPT emphasizes the therapeutic relationship and self-esteem as vehicles for patient improvement.^{115,116} Session content may include discussion of relationships and emotions (related and unrelated to RNT symptoms). SPT therapists take an empathic and validating stance so that patients are comforted when upset and supported when coping with distressing feelings. Specific SPT techniques include communicating positive regard for the patient through verbal and nonverbal behavior; using a relaxed conversational style in the therapy; providing empathy, praise, and encouragement; clarification; ventilation (allowing the patient to express intense feelings); and absolution (i.e., normalizing minor inadequacies to eliminate guilt).

Adjunctive Services and Attrition Prevention (ASAP)

In addition to the scheduled AR-ERT and SPT sessions, each participant will be permitted up to two ASAP sessions. An ASAP session addresses subject crises or unusual circumstances/needs that may arise, with the goal of subject retention. This strategy has been implemented successfully in other large federally funded randomized controlled trials in our clinic.

6. BIOSTATISTICAL ANALYSIS

Overview

Data acquisition and analytics approaches will be performed by Dr. Jacoby under the supervision of biostatistician Dr. David Schoenfeld. To characterize our sample, data will be displayed graphically, and summary statistics (e.g., means and frequencies) will be calculated for all variables, including demographic and clinical descriptors. Descriptive statistics and exploratory graphing (e.g., scatter plots) will be used to assess normality, skew, and outliers on all measures. Continuous measures will be transformed if necessary, to satisfy assumptions of normality and homogeneity of variance.

Baseline differences between the treatment arms (AR-ERT vs. SPT) in demographic and other potential prognostic variables will be examined using chi-square analyses for discrete variables and ANOVA for continuous variables. While randomization tends to produce well-balanced treatment samples, if we find significant differences in potentially important baseline variables, we will include these variables as covariates in subsequent multivariate analyses. Candidate covariates for adjustment include baseline values of RNT (PTQ-PW score), symptom measures (Y-BOCS, SIGH-A, SIGH-D), and use of psychotropic medication (yes/no). Additional covariates that are unlikely to moderate treatment effect, but nonetheless will be examined for completeness, include: age, gender, education, race/ethnicity (majority vs. minority as we do not anticipate recruiting enough subjects from any one minority group to perform analyses for specific groups). If effects of gender and/or minority status are found that might be clinically meaningful, even if not statistically significant, we will report these to guide future research. Frequencies of adverse events (with 95% confidence intervals) will be calculated by treatment arm and type of event. We also will compare treatment groups on baseline credibility/expectancy of treatment and post-treatment satisfaction. A two-tailed p value $<.05$ will be considered evidence of statistical significance for the primary outcome.

Missing Data

Our multi-level generalized linear modeling (GLM) approach (described below under “Primary Analyses”) uses an intent-to-treat analysis that includes all participants, regardless of missing data (increasing power and generalizability), and it provides accurate estimates of regression coefficients in small samples.^{118,119} Despite our best efforts to retain participants, we do expect dropouts (i.e., subjects who are lost to follow-up or withdraw early from the study for reasons described below under “Participant Withdrawal”). We will attempt to perform all scheduled assessments for subjects who are withdrawn from the protocol and will provide financial incentives for participation in assessments.

Missing data rates and patterns will be assessed by treatment arm. Reason(s) for missing data will be documented, and we will evaluate reasons for dropout, study withdrawal, and loss-to-follow-up by treatment group. We will attempt to ascertain if missingness is occurring at random by evaluating factors associated with dropout for potential attrition bias. We will also compare study dropouts to study completers on demographic and clinical variables. Finally, we will use sensitivity analyses to quantify the impact of missing data.¹²⁰

Data Processing

For behavioral tasks that include reaction times (e.g., the Emotional Interference Task [EIT]), we will remove reaction times <150 ms given that such responses are rare and likely represent errors.¹²¹ Eye position fixations from the Attentional Engagement-Disengagement Task (AEDT) sampled at 120Hz will be converted to visual fixation data using standard criteria (i.e., minimum duration 100ms; minimum radius 1 degree).¹²²

Eye-blink artifacts will be removed from scalp-recorded EEG data on the Cued

Emotional Control Task (CECT) and during the resting-state period (0.1-100Hz, sample rate = 256Hz) using established procedures,¹²³ and gross artifacts will be rejected by visual inspection. For the CECT, cue- and target-locked event related potentials (ERPs) will be formed by segmenting EEG data around cue and stimulus onsets (from -200 ms to 1000 ms post-stimulus) and averaging the segments. Start and end points for the components of interest are: (a) cue-locked N2: 200-350ms post-cue; (b) target-locked N2: 200-350ms post-target; (c) target-locked N450: 400-500ms post-target; (d) target-locked P300: 300-600ms post-target.⁴⁹ ERPs will be rejected if there is significant artifact (e.g., amplitude $\pm 100 \mu\text{V}$) at any electrode on a given trial. Artifact-free mean amplitudes (μV) will be extracted for ERP analyses. Additionally, nonoverlapping, artifact-free 2-second epochs from the resting-state period will be extracted for source localization analyses. Building on recent source localization studies,^{80,124} seeds from key regions within the frontoparietal (FPN) and default mode (DMN) networks will be selected to create regions of interest (ROIs) based on previous published methods^{125,126} and drawing from the Montreal Neurological Institute 305 template.¹²⁷ We will then compute EEG source-based functional connectivity using exact Low Resolution Electromagnetic Tomography (eLORETA) software.⁷⁸

Primary Analyses

Due to the nested structure of the data (i.e., 4 assessments per participant), we will use a multi-level generalized linear modeling (GLM) approach to address each of our hypotheses.

Hypothesis 1: Target Engagement. To test whether participants who receive AR-ERT show greater improvements in attentional/cognitive control relative to those who receive SPT, we will run a series of GLM analyses for each index of our attentional/cognitive control target:

- 1) **Behavioral:** (a) attentional disengagement (i.e., latency of shift in gaze from emotional to neutral face surrounded by the frame; AEDT), and (b) sustained attention (i.e., difference in reaction times to tones following a negative vs. neutral stimulus on the EIT),
- 2) **Electrophysiological:** (a) proactive cognitive control in anticipation of conflict (i.e., cue-locked N2 ERP amplitudes on “opposite” vs. “actual” trials; CECT), and (b) reactive cognitive control in response to conflict (i.e., target-locked N2, N450, and P300 ERP amplitudes after the “opposite” vs. “actual” cue; CECT),
- 3) **Self-report:** Attentional Control Scale (ACS).

We will analyze each target index individually without adjusting for multiple testing¹²⁸ in order to be inclusive in identifying targets for future studies (e.g., R61/R33 proposal). Analyses will be modeled as the GLM equivalent of 2 x 3 ANOVAs with treatment condition (AR-ERT vs. SPT), time (pre-, mid-, post-treatment), and their interaction as fixed effects; the primary contrast of interest will be treatment difference at week 8 (post-treatment).¹²⁹ Repeated measures per person will be modeled with either an auto-correlation, Toeplitz, or unstructured covariance matrix (choosing the best model based on AIC and BIC).

Hypothesis 2a: Treatment Efficacy. To examine whether repetitive negative thinking (RNT) and psychiatric functioning improve during AR-ERT, we will also use GLM. Analyses will be modeled as the GLM equivalent of 2 x 4 ANOVAs with treatment condition (AR-ERT vs. SPT), time (pre-, mid-, post-treatment, follow-up), and their interaction as fixed effects; the primary contrast of interest will be treatment difference at week 8 (post-treatment), and a secondary outcome contrast will be at week 20 (3-month follow-up). Outcomes include:

- 1) **Repetitive Negative Thinking:** (a) Perseverative Thinking Questionnaire – Past Week (PTQ-PW; primary outcome), (b) Rumination Response Scale (RRS), (c) Penn State Worry Questionnaire (PSWQ), and (d) Rumination on Obsessions and Compulsions Scale (ROCS).

- 2) **Clinical Symptoms:** (a) Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Dimensional Obsessive-Compulsive Scale (DOCS), (b) Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) and State Trait Anxiety Inventory-Trait (STAI-T), (c) Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) and Beck Depression Inventory (BDI-II), and (d) Clinical Global Impression Scale – Severity (CGI-S).
- 3) **Psychiatric Functioning:** (a) Work and Social Adjustment Scale (WSAS), and (b) Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF).

Hypothesis 2b: Target Validation. To examine the extent to which alteration in the hypothesized target (attentional/cognitive control) is related to improvements in clinical RNT outcomes, we will compute change scores from pre- to post-treatment for both the target (i.e., AEDT, EIT, CECT, ACS) and outcome measures (i.e., PTQ-PW [primary outcome], RRS, PSWQ, ROCS, Y-BOCS, DOCS, SIGH-A, STAI-T, SIGH-D, BDI-II, CGI-S, WSAS, Q-LES-Q-SF). Pearson's correlations between changes in target and changes in outcome measures will then be computed (i.e., a completers-only analysis).

Exploratory Source Localization Analyses

We will also conduct exploratory source localization analyses with a focus on the frontoparietal (FPN) and default mode (DMN) networks. Based on previous research demonstrating changes in the anterior cingulate cortex (ACC) over the course of psychosocial treatment^{130,131} and indicating that increased activity in this region predicts better treatment outcomes,^{79,132–134} we will test the following:

1. Whether changes in ACC activation are demonstrated pre/post treatment using GLM (i.e., predicting a main effect of time) and whether treatment group (AR-ERT vs. SPT) moderates this effect (i.e., treatment group x time interaction).
2. Whether baseline (week 0) rostral ACC (rACC) theta (4.5-7 Hz) current density predicts greater reduction in RNT and symptom severity as measured by the PTQ-PW and disorder-specific measures using GLM (i.e., predicting a rACC theta x time interaction) and whether treatment group (AR-ERT vs. SPT) moderates this effect (i.e., treatment group x rACC theta x time interaction).

Finally, source localization analyses will be used to investigate the neural generators of scalp-recorded EEG signals during the CECT, with a focus on the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC) given their roles in conflict monitoring (dACC) and conflict resolution (DLPFC), respectively.^{57,58,135–139}

Power Analysis and Sample Size

In prior studies,^{31,140} ERT significantly improved mean levels of attentional control (ACS, our self-report target; 15.6%) and reduced RNT (PTQ-PW, our primary outcome; 37.2%) from pre- to post-treatment; with effect sizes of Hedge's $g = 1.65$ and 2.36 respectively in an open trial. ERT also significantly reduced worry (PSWQ; 34.8%) and rumination (RRS; 17.6%); with effect sizes of Hedge's $g = 1.50$ and 0.74 respectively compared to a waitlist control group with contact. Our electrophysiological and behavioral targets of attentional/cognitive control have also demonstrated sensitivity to intervention in previous studies.^{40,77,141} Sixty-two patients with elevated RNT (to balance power with recruitment feasibility) will enter the study to have a sample of 52 with attrition, which is reasonable given previous 85% retention rates of ERT at post-treatment (our primary endpoint).³¹ Based on power calculations (i.e., one-way ANOVA at post-treatment, assuming a 1:1 randomization to AR-ERT vs. SPT), with $n = 52$ completers, we will have 80% power to see a difference at .05 sig. level if the true effect size is 0.8 or greater

which is within range of the previous studies cited above. Finally, with 52 people at the end of treatment, we can detect correlations between target and outcome measures of .38 or greater.

7. RISKS AND DISCOMFORTS

The following are potential risks/discomforts that participants may experience in this study:

- 1) **Assessments and Questionnaires.** During the study assessments, participants may feel bored or tired completing some of the questionnaires or computer tasks. They also might experience some discomfort, embarrassment, or anxiety from discussing personal material and completing self-report questionnaires. Likewise, some participants may feel uncomfortable about having assessment sessions digitally recorded and reviewed by study staff (which is necessary for rater supervision as well as assessment of the reliability of ratings).
- 2) **EEG.** There are no known or foreseeable risks or side effects associated the EEG procedures. The EEG sensors (Brain Products GmbH, Gilching, Germany) have been approved by the U.S. Food and Drug Administration (FDA) for research purposes and will be operated within the standards reviewed and accepted by the FDA. Participants may experience some discomfort because we may have to gently scrape the skin in order to receive clear signals from the EEG electrodes.
- 3) **Computer tasks.** Some of the scenes that participants will view during the Emotional Interference Task (EIT) involve emotionally evocative images of violence, death, blood/gore, and sex (from the International Affective Picture System [IAPS] dataset) and may generate distress.
- 4) **Treatment.** The treatment offered in this study may make some individuals temporarily distressed during procedures that involve confronting the content of their repetitive negative thoughts and associated emotions of depression and anxiety (e.g., mindfulness of thoughts and emotions; imaginal rehearsal tasks); however, these procedures rarely make subjects significantly distressed, and participants will be able to manage the intensity of these exercises along with their therapist. Participants may also experience an increase in distress due to the natural waxing and waning of OCD, anxiety, and depression symptoms; however, participants will be carefully monitored, and measures will be taken to minimize potential risks during the project period (as discussed in "Protection Against Risks" below).
- 5) **Privacy and Confidentiality.** Breach of confidentiality represents a potential risk; however, the greatest care will be taken to prevent this from occurring (as discussed in "Protection Against Risks" below). In the informed consent process, we will also inform participants of the legal limits to privacy and confidentiality including: (1) if we believe participants are at serious risk of harming themselves or another person, (2) if we learn of ongoing abuse or neglect of a child, disabled, or elderly person, and (3) if we receive a subpoena or court order. We currently have an active Business Associate Agreement with a Statement of Work for iMotions Inc to be able to share coded data collected and analyzed using their software platform (i.e., the eye tracking data) for data support purposes.

In addition to the above practices, our study will be under compliance with the HIPAA (Health Insurance Portability and Accountability Act) rules governing the Partners

Healthcare system. All participants who enroll in this study will be given an electronic copy of the HIPAA privacy notice and will be asked to sign an acknowledgement of receipt and authorization form.

Protection Against Risks

The following procedures will be implemented to protect participants against risks:

- 1) **Informed Consent.** Informed consent will be obtained at the virtual screening visit using IRB-approved e-consent forms. After participants read the consent form, the PI (Dr. Jacoby) or doctoral-level delegate will paraphrase each segment of the consent form and answer any questions. Participants will be clearly informed of the voluntary and confidential nature of their participation, the potential risks and benefits of the study, and their right to terminate treatment at any time without penalty. There will be a clause included in the informed consent form concerning the audio taping of assessments and therapy sessions for reliability. As of February 2022, participants will be shown sample images from the IAPS database so they can decide whether to participate in the EIT task since the images may be distressing. Participants already enrolled prior to this change will not be re-consented because they have already seen the task and know what it entails. If the participant agrees to participate in the study, the consent form will be signed by the research participant and the PI using the e-consent module in REDCapTM. Each participant will be emailed a copy of the signed and dated consent forms.
- 2) **Assessments and Treatment.** The IEs will make every attempt to help participants feel comfortable when discussing sensitive material. Participants will have as much time as needed to complete study questionnaires and may skip any questions they do not want to answer. The therapist will work with the participant to ensure sessions are tolerable and appropriate in terms of risk and distress.
- 3) **EEG.** The experimenters will make every attempt to help participants feel comfortable during the EEG and will check in with participants regarding their comfort level during the set-up of the EEG sensors. Participants can ask to pause or stop the EEG session at any time, for any reason.
- 4) **Computer tasks.** Participants will be shown two sample images from the same database at the screening visit so they can decide whether to participate in the EIT. If they choose to participate in the task, they are also told that it is alright to look away during the task if they find these images too disturbing.
- 5) **Privacy and Confidentiality.** The following methods will be used to protect the confidentiality of information provided by participants:
 - a) Data will be encoded using Participant IDs and not names. IDs will be assigned sequentially and unrelated to name, social security number, or other easily identified information.
 - b) Names will not be included in digital recordings, in computerized data files, or in any published reports.
 - c) Digital recordings for reliability, adherence, and competence will be stored securely in a password-protected drive within the Center for OCD and Related Disorders and destroyed after completion of the study.
 - d) Study data will be reviewed only by pre-designated study personnel or, if necessary, by institutional, state or federal regulatory personnel.

- e) All personnel will be trained in research confidentiality procedures and will be educated about the importance of strictly protecting participants' rights to confidentiality.
 - f) Many procedures will be used to protect the security of data collected via REDCapTM, the platform for electronic data capture that will be used in this study. REDCapTM is deployed on a secured server. All network connections to the server are encrypted using high strength cyphers of at least 128 bits. The hardware is owned by MGH/Harvard Medical School (HMS) and administered by several computer professionals employed by the MGH/HMS.
 - g) MGH is accredited by the Association for the Accreditation of the Human Research Protection Programs Inc. (AAHRP), indicating that it is an institution that has regulations and policies in place to ensure protection of research participants and their confidentiality that exceed federal requirements for safeguarding participants.
 - h) Data shared with iMotions Inc for data support purposes will only include participants' coded alphanumeric study IDs and the key to the coded data (linking study ID and participants' identifiable information) will not be shared. Thus, iMotions will not have the ability to link the data to individual participants. Files will be shared via PHS Secure File Transfer.
 - i) Any data that is shared with other collaborators in the future would only be done so after executing a formal Data Use Agreement from Massachusetts General Hospital (MGH). As part of this process, the final dataset would be stripped of any identifiers that would permit linkages to individual research participants prior to release for sharing (i.e., coded). Additionally, given the sensitive nature of psychiatric symptoms and diagnosis and our relatively small sample size, we would make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a well-described justification for the use of the data; (2) a commitment to using the data only for research purposes (under purview of an institutional IRB) and not to identify any individual participant; (3) a commitment to securing the data using appropriate computer technology; (4) a commitment to not transfer the data to other users; and (5) a commitment to destroying the data after analyses are completed. In compliance with NIH guidelines, data sharing would be done in a timely fashion (i.e., no later than the acceptance for publication of the main findings for the final dataset).
 - j) Due to the NIH-funding for this study, a Certificate of Confidentiality will automatically be obtained.
 - k) All necessary precautions will be taken to ensure participant privacy while conducting virtual study visits over ZoomTM. Healthcare Secure ZoomTM includes built in protections such as chat encryption, mandatory waiting rooms, and disablement of video recordings.
- 6) Emergencies and Suicidality.** Because patients with affective disorders can also experience suicidal thinking and behaviors, we will carefully implement safety precautions including:
- a) Patients who are actively suicidal at the screening visit (as assessed by the SCID-5-RV, SIGH-D, and/or score on the BDI-II suicide item #9 ≥ 2) will be excluded from the study.
 - b) Screening procedures will also exclude any individuals at potentially greater risk for psychiatric deterioration or an adverse outcome, or who are not clinically suitable for the study protocol. For example, as described in the

inclusion/exclusion criteria above, individuals will be excluded if they have active and clinically significant homicidality or any features requiring a higher level of care.

- c) As part of the informed consent process, participants will be asked if they are willing to provide contact information for two friends or family members and to give permission to have the research team call or write to these individuals in the case of an emergency (i.e., if we have concerns about their wellbeing).
 - d) Suicidality will be closely monitored with the BDI-II suicide item (#9) and clinician inquiry at each visit.
 - e) Patients at higher risk will be withdrawn from the study as described in the next section below.
 - f) Dr. Jacoby (or covering clinician in her absence) will be available 24/7 to participants in the event of a clinical emergency; this will be clearly communicated orally and in writing to study participants (i.e., the consent form describes how to reach the investigators in an emergency). Participants will be referred for a higher level of care as needed.
 - g) In the event that a study staff member witnesses behaviors such as abuse or neglect of children or the elderly while conducting a virtual study visit via Zoom™, they will report this to the PI who will consult with the Office of General Council and follow hospital policy for reporting such behaviors.
- 7) **Participant Withdrawal.** Subjects may be withdrawn from the study for *any* of the following reasons:
- a) A significantly deteriorating clinical course, such as emergence of active suicidal ideation or a need for hospitalization.
 - b) Score of ≥ 2 on the BDI-II suicide item (#9) and subsequent evaluation by the PI indicating it would be unsafe for the patient to remain in the study.
 - c) Score of 6 (much worse) or 7 (very much worse) on the CGI-I for 3 consecutive weeks and therapist and PI judgment that remaining in the study is not in the subject's best interest; a patient may be withdrawn sooner than this, if in the judgment of the therapist and PI, this is in the patient's best interest.
 - d) PIs' decision that withdrawal from the study is in the subject's best interest.
 - e) Subject's decision to withdraw.

Subjects who require medication changes or begin other types of therapy (e.g., family therapy) will be kept in the study even though such events violate study procedures. We will compare outcome data for compliant and non-compliant subjects.

The PI will discuss and agree upon the withdrawal of any subject with the therapist and Dr. Wilhelm. The reason for withdrawal or dropout will be documented, and the subject will be referred for appropriate treatment. Except for subjects who withdraw consent to participate, all who are withdrawn or drop out of the study will be asked to complete all remaining assessments. We will educate subjects about the importance of completing all scheduled assessments and will provide payment as described above to encourage retention. As mentioned above, participants will be asked if they are willing to provide contact information for two friends or family members and to give permission to have the research team call or write to these individuals if contact between the participant and the research team is lost.

The above procedures have been used in previous research studies and were effective in protecting our research participants against risk. Therefore, we anticipate that these procedures

will be effective in our proposed study. In the unlikely event that a participant experiences a research-related injury, the study PI will arrange for appropriate treatment.

8. POTENTIAL BENEFITS

Participants may benefit from the comprehensive diagnostic assessment provided at the outset of the study. Patients with RNT may also benefit by experiencing relief from their symptoms. For participants assigned to AR-ERT, this treatment includes elements that have been shown to lead to decreased symptomatology in mood and anxiety disorders, and to improve quality of life and functional impairment. For participants assigned to SPT, this therapy is commonly offered by community clinicians for affective disorders, and thus is comparable to services patients might receive elsewhere. SPT is also acceptable from a safety perspective, as it allows for close monitoring.

Indirect benefits of the study include increased knowledge regarding treatment for RNT that will improve interventions for future patients and decreased impact of psychiatric illnesses characterized by RNT on society (i.e., reduced health care costs and disability). The knowledge to be gained by the proposed research has enormous public health importance because RNT is highly prevalent in the general population, and excessive healthcare costs are being spent on treatments that are not optimally effective. Mood and anxiety disorders are among the most common and disabling mental health conditions world-wide, and given their high comorbidity, prioritizing the understanding and treatment of shared characteristics like RNT may lead to more efficacious interventions for a broader range of patients. Although cognitive behavioral therapy is considered an effective first line intervention, many patients receiving this treatment are deemed non-responders, suggesting that underlying factors – such as RNT, which remains a residual symptom – are not being fully addressed. Thus, by engaging biobehavioral targets of attentional/cognitive control posited to underlie RNT and measuring target engagement and validation of this mechanism with a multi-method approach (i.e., ERPs, eye tracking), this study has great potential to improve the precision of RNT and emotion-focused therapies for affective disorders.

The risks that this study poses to participants are reasonable in relation to the importance of knowledge that may be expected to result because psychiatric disorders characterized by RNT are common, can be severe, and are often chronic. Thus, risks of discomfort associated with treatment are offset by the potential benefit of reduction of symptoms and improvement in mood, functioning, and quality of life for these patients. As such, the benefits of this study far outweigh the potential risks.

9. MONITORING AND QUALITY ASSURANCE

Therapist Training and Supervision

All treatment will be provided by masters- or doctoral-level mental health professionals experienced in cognitive behavioral techniques like AR-ERT, experienced in SPT, and familiar with affective disorders. We carefully considered the advantages and disadvantages of therapists providing one treatment but not the other (nesting within conditions) versus providing both treatments (crossing therapists with conditions).¹⁴² To assure equivalence of therapist training and competence, study therapists will provide therapy to patients in both conditions (AR-ERT and SPT).

Therapists will receive rigorous training before treating study patients. First, therapists will read the treatment manuals, related reading materials on AR-ERT and SPT, and readings on RNT. Therapists will then have to pass (i.e., 90% correct) a knowledge test about their

reading material. Therapists will attend a training led by Dr. Jacoby that consists of: (1) a discussion of the phenomenology and other important aspects of RNT, (2) an overview of implementation of the study protocol, (3) training on the manualized treatments, which will include slide presentations, role plays, and discussion, and (4) a discussion of the distinctiveness of the two treatments. To ensure ongoing high-quality treatment, therapists in each condition will receive weekly supervision from the PI (Dr. Jacoby) in AR-ERT and SPT. Care will be taken in supervision to ensure that specific AR-ERT techniques are not introduced into SPT.

Monitoring of Treatment Fidelity

All treatment sessions will be digitally audio recorded. A doctoral-level independent adherence rater will rate 5% of randomly selected sessions at regular intervals during the study using our adherence and competence measures described above. This will be done to ensure adherence to the treatment manuals (to minimize the risk that techniques implemented in AR-ERT are delivered in the SPT condition; i.e., therapist drift), consistency of treatment delivery, and competent delivery of the treatments. The adherence rater will have experience with both AR-ERT and SPT and will be further trained and supervised by Dr. Jacoby. He/she will attend the initial therapist training activities described above and will watch the training tapes of AR-ERT and SPT. Descriptive statistics on adherence and competence ratings will be obtained.

Independent Evaluator (IE) Qualifications and Ensuring IE Blindness

A blinded evaluation of outcomes by an IE is essential to obtain unbiased information on treatment efficacy. IEs will have a masters or doctoral degree in psychology or a related mental health field. We will take many steps to ensure that IEs remain blind to treatment condition throughout the study for all participants. IEs will not be told the treatment assignment for any participant. IEs will be trained to focus on outcome measurement only and to avoid any discussion of what treatment subjects are receiving. Moreover, patients will be reminded at each IE assessment not to discuss their treatment with the IE. Therapists and study staff will be regularly reminded of this as well. Supervisory discussions about treatment will occur in separate meetings attended only by therapists and supervising clinicians. Treatment and assessment recordings will be kept in separate locations. Furthermore, the IE will be asked to guess the treatment condition of each participant after the completion of the follow-up assessments or, for dropouts, after the last treatment session.

Establishing and Monitoring Interrater Reliability

The study team has extensive experience with the measures used in this study. Training and reliability checks will be done to ensure that IEs conduct ratings in a uniform way. IEs will first receive instruction in the Y-BOCS, SIGH-A, SIGH-D, and CGI-I/S from Dr. Jacoby in an initial study start-up meeting. Subsequently, IEs will rate Y-BOCS, SIGH-A, SIGH-D, and CGI-I/S training tapes of interviews conducted by Dr. Jacoby. IEs will be certified when they reach reliability criteria with Dr. Jacoby for these measures (defined by ICCs $\geq .8$).

To maintain inter-rater reliability during the study and reduce rater drift, all assessments will be audio recorded. A senior member of the OCD Program's staff will review and rate 5% of randomly selected digitally recorded interviews at regular intervals during the study. If reliability with this rater falls below the above criteria, we will institute retraining procedures. Dr. Wilhelm will also conduct weekly supervision meetings with IEs during which assessment interviews from the past week will be discussed. Any problems in interview content and diagnostic disagreements will be addressed during supervision. Reliability statistics will be included in our publications.

Research Team Meetings

In addition to the study start up meetings described above, the PI and clinical research assistant will meet weekly to discuss the study, including recruitment, new subjects to ensure inclusion/exclusion criteria are met, withdrawal of any subjects, any safety issues, and other topics.

Data and Safety Monitoring Board (DSMB)

In order to provide the most comprehensive protection of participants, we will establish a formal data and safety monitoring board (DSMB). The DSMB will be comprised of 3 members who have expertise in clinical trials, anxiety, mood, and OC spectrum disorders, are not affiliated in any other way with the proposed project, and do not have an affiliation with the MGH/Harvard Medical School. Board members will consist of:

- 1) Eric Storch, Ph.D., Professor of Psychiatry and Behavioral Sciences, Baylor College of Medicine
- 2) Alicia Meuret, Ph.D., Associate Professor in Clinical Psychology and Director of the Anxiety and Depression Research Center at Southern Methodist University
- 3) Adam Lewin, Ph.D. Associate Professor and Director OCD & Related Disorders Program, University of South Florida

All board members are very familiar with safety and ethical concerns related to human subjects in clinical research. The DSMB will meet twice per year (by conference call) to review the study's progress, enrollment, deidentified group-level data for differential rates in key outcomes, and adverse events. They will be responsible for monitoring rates of enrollment and study retention, patient safety, and data confidentiality and entry. The DSMB will provide guidance to the PI (Dr. Jacoby) who will then be responsible for executing the data and safety monitoring plan and complying with the reporting requirements. The PI will provide a summary of the DSMB report to the NIH on an annual basis as part of the progress report. The DSMB report will include participants' sociodemographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events, and any actions or changes with respect to the protocol. The DSMB report will include, when available, the results of analyses that have been conducted.

Adverse Events Reporting

Based on information from previous studies involving EEG, clinical assessment, and treatment, the following adverse events are expected, as described in the consent form and reviewed in detail above in Section 3C:

1. Becoming tired or uncomfortable answering assessments and questionnaires
2. Discomfort from scraping skin on the scalp during EEG procedures
3. Distress from the computerized images during the eye-tracking task
4. Temporary increase in anxiety or depression during treatment
5. Possible loss of privacy (e.g., due to contacting an emergency-contact or due to legal limits of confidentiality)

An IRB approved AE Tracking log will be administered by the RA and reviewed by the PI at the clinical assessment visits (baseline, mid-treatment, post-treatment, and 3-month follow-up) to probe for any adverse events that occurred since the last visit.

Adverse events and Unanticipated problems will be reported to the MGB IRB in accordance with its policy. Specifically, in accordance with guidelines of the Office for Human Research Protections (OHRP) and NIMH, reporting of adverse events will occur to (1) the MGH IRB, (2) the NIMH program officer, (3) OHRP, and (4) the DSMB as follows:

- 1) Unexpected **serious adverse events** (SAE) related to study participation (e.g., death, life threatening AE, suicide attempt, inpatient hospitalization) will be reported within **5 business days** of the study team first learning of a death and within **10 business days** of the study team becoming aware of a non-death SAE.
- 2) Any **other unanticipated problems** involving risks to subjects or others will be reported within **10 business days** of the study team becoming aware of the event.
- 3) All **adverse events** and SAEs that are deemed expected or unrelated to the study will be summarized in **twice-annual progress reports** for the DSMB and in **annual progress reports** for the NIMH and IRB.

Documentation to be submitted for reportable events will include:

- Identifying information for the research protocol (e.g., project title, investigator's name, and the grant/contract number)
- The date on which the event occurred and the date at which the PI became aware of the event
- A detailed description of the event and impact on the participant(s)
- A detailed description of the measures taken (including clinical) in response to the event (if any)
- Confirmation that the appropriate monitoring entities and regulatory bodies have been notified as needed
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the event

Data Management

REDCap™ (Research Electronic Data Capture) is a free, secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data collection projects rely on a study-specific data dictionary defined by members of the research team with planning assistance from Harvard Catalyst | The Harvard Clinical and Translational Science Center EDC Support Staff. The iterative development and testing process result in a well-planned data collection strategy for individual studies. Using REDCap, the research team can also design web-based surveys and engage potential respondents using a variety of notification methods. REDCap provides flexible features that can be used for a variety of research projects and provides an intuitive interface to enter data with real time validation (automated data type and range checks). The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Scales are completed securely via the internet by using any device with standard web access and browsers. Participants and/or research staff will enter scale responses directly into REDCap electronic assessment forms. Using 256 bit RSA Secure Socket Layer (SSL) encryption, approved users will be logged-in to machines using secured browsers behind the Partners Healthcare Systems IS corporate firewall. Staff will have a unique identifying key that will link them to the electronic study forms. This unique ID will be used in addition to a randomly

generated secure password that only the staff person will have. Thus, under supervision by staff, each subject will only have access to complete his/her own scales and will not be able to view data from any other subjects.

Responses entered by subjects will be transmitted to and stored in a secured database at MGH. This database will be configured in REDCap by the database administrator who will set up strict permissions to maintain confidentiality. Dr. Susanne Hoeppner will assist with creating logical checks to identify data inconsistencies, omissions, and errors in real-time. Issues identified will trigger queries, and problems will be resolved promptly. Emails will be automatically sent to research assistants when scales are completed so any missing data can be examined. Data will be backed up automatically nightly and downloaded from REDCap into SPSS for analysis.

Data collected from two instruments will be stored outside of the REDCap™ system. Specifically, data collected at screening from the clinician-administered computerized SCID-5-RV (NetSCID-5) will be saved within the TeleSage, Inc. system. TeleSage, Inc. ensures the privacy and confidentiality of NetSCID data using a rigorous set of procedures. Each participant is associated with a unique NetSCID project and its affiliated organization, as well as a coded participant ID. All data are stored on a Secured Socket Layer (SSL) HIPAA-compliant web server, encrypted at rest and geo-redundant data backup on a separate HIPAA-compliant database. Data is downloaded in encrypted format by users via a secure data download page. In addition, participant responses on the BDI-II at the 3-month follow-up time-point will be stored electronically utilizing the Q-global software system by Pearson, Inc. All data will be coded using a corresponding participant ID and stored on Pearson's servers or those of its affiliates and/or authorized vendors and will only be accessible by authorized employees, agents and contractors of Pearson and its affiliates and authorized vendors.

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