

Developing Effective Response Inhibition Training for Symptom Relief in OCD and Trichotillomania

NCT02059980

7/1/2018

STUDY PROTOCOL

Effective behavioral and pharmacological treatments exist for obsessive-compulsive disorder (OCD), but a significant portion of patients with OCD refuse to receive, drop out of, or otherwise fail to respond to the currently most efficacious treatments.^{1,2} Suboptimal clinical outcomes and under-utilization of these treatments often result from practical barriers such as adverse effects (e.g., intense distress during the exposure procedure or side effects of medication), high costs, and a lack of trained therapists.³ Despite the demonstrated efficacy of existing treatments, almost half of individuals with OCD continue to suffer from this extremely debilitating condition without adequate treatment. Thus, disseminable and cost-efficient therapeutic approaches with minimal adverse effects are required for OCD. In this regard, a promising therapeutic approach is computerized cognitive retraining which has recently shown success in improving psychiatric conditions by directly modifying biased or deficient cognitive processes that are considered to be central to such conditions.⁴⁻⁶ There is compelling evidence that poor response inhibition (RI) is a core cognitive feature of OCD^{7,8} and is its putative endophenotype.⁹ RI is the basic cognitive ability required to inhibit potent but inappropriate responses,¹⁰ and research indicates that RI can be functionally changed by practice.¹¹ Despite the growing evidence for the significance of poor RI in OCD, it is unknown whether OCD symptoms can be improved using cognitive retraining designed to enhance the individual's RI capabilities. To improve overall treatment response rates in OCD, it is vital to develop an effective intervention with minimal adverse effects that may result in enhanced treatment acceptability, patient retention, and dissemination.

Our long-term goal is to understand how to change anomalous cognitive processes underlying OCD and its related conditions such as trichotillomania (TTM) in order to develop and disseminate effective computer-based cognitive interventions. The objective of the current R21 application is to examine the feasibility of using a computerized RI training (RIT) program to improve OCD-related symptoms. Our central hypothesis is that cognitive training designed to enhance RI will improve this problematic cognitive process in OCD and TTM and produce a significant reduction in OCD/TTM symptoms. This hypothesis is based on (a) existing behavioral, electrophysiological, and neuroimaging data suggesting poor RI as a core feature of OCD and TTM and (b) our preliminary data suggesting that RIT can be a useful therapeutic intervention for OCD and its related conditions characterized by poor RI. The expected results will lay a strong groundwork for future studies at the R01 level aimed at developing, testing and disseminating evidence-based RI-focused cognitive training for OCD that can be used as an adjunctive intervention to enhance existing treatments or as a stand-alone intervention. We propose two specific aims and an exploratory aim for this proposal.

Aim 1. To determine the effectiveness of computerized RIT in enhancing RI among OCD/TTM patients.

We hypothesize that OCD/TTM patients who undergo the 8-session RIT program will show greater RI capabilities, relative to OCD/TTM patients who receive placebo cognitive training.

Aim 2. To determine the utility of computerized RIT in improving OCD/TTM symptoms. We hypothesize that OCD/TTM patients who undergo the 8-session RIT program will show a greater reduction in OCD/TTM symptoms, relative to OCD/TTM patients who receive placebo cognitive training.

Exploratory Aim. To evaluate the subjective treatment experiences and patient retention. To assess the end-user acceptability of the proposed cognitive training program, we will assess treatment acceptability and satisfaction as well as treatment refusal and drop-out rates.

This project is innovative because it uses the approach of a novel cognitive training intervention to directly modify underlying cognitive abilities and improve OCD symptoms. The proposed RIT program has been designed as an engaging and immersive computer game to target a core cognitive deficit of OCD-related conditions, which is also in line with the NIH's growing interest in computer game-based neuropsychiatric intervention. This project is expected to have a positive impact by generating important knowledge that will guide the development of an effective cognitive training program for OCD-related conditions that would potentially result in an effective, cost-efficient, and portable intervention with low adverse effects, or enhance the clinical outcomes of existing treatments as an adjunctive intervention. If successful, this line of translational research is expected to contribute to improving overall treatment response rates among individuals suffering from this debilitating and costly illness, yielding significant public health impact.

APPROACH

Project Overview. Over the course of 2 years, 30 individuals with OCD/TTM will complete either RI Training (RIT; n=15) or Placebo Training (PLT; n=15). At baseline, participants will complete (a) clinician-administered rating and self-report scales for OCD/TTM symptoms, (b) questionnaires for other emotional symptoms, and (c) 3 RI assessment tasks. Participants will then undergo 8-session cognitive training (RIT or PLT) over a 4-week period. Both participants and the independent evaluator (IE) will be blinded to the training condition. Potential adverse events will be assessed weekly during the intervention period by the IE. At post-training, we will re-evaluate participants' symptom severity and RI performance. Treatment acceptability and satisfaction will also be measured at this point. At 1-month follow-up, participants will be assessed again for the severity of OCD/TTM and other emotional symptoms and RI performance (see Figure 1). Regarding the overall timeline of the project, active recruitment will occur in Month 2 through 22 after the initial preparatory work (Month 1). Data analyses and preparation of manuscripts, conference presentations, and a grant application will occur in Month 20 through 24.

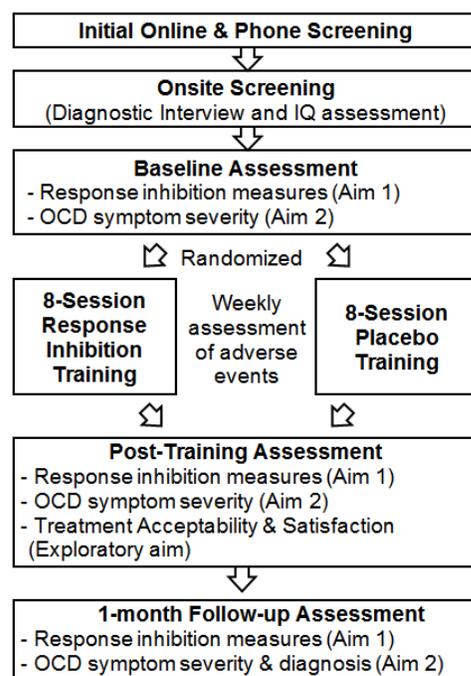


Figure 1. Overall Study Procedures

RESEARCH DESIGN

Participants. We will recruit 30 individuals who meet the following inclusion criteria: (a) age between 18 and 60, (b) a primary diagnosis of OCD/TTM as determined by the Structured Clinical Interview for DSM-5 (SCID-5), (c) moderate level of OCD or TTM symptoms,⁴⁷ and (d) IQ > 80 (on the Wechsler Abbreviated Scale of Intelligence-II). Exclusion criteria include: (a) current substance abuse/dependence, (b) current or past psychotic disorder, bipolar disorder, or schizophrenia, (c) presence of ADHD, or TS (conditions known for poor RI), (d) severe depressive symptoms (evidence suggests that executive function deficits in OCD are attributable to comorbid depression^{48,49}), (e) current psychotherapy, (f) current psychoactive medications (a variety of pharmacological agents were shown to be implicated in RI, including dopamine, norepinephrine, and serotonin⁵⁰⁻⁵²), and (g) current suicidality.

Cognitive Training Programs. RIT is a 30-level computer game (with a story of defending a village from aliens), designed to offer systematic practice of RI focused primarily on action withholding and cancellation, incorporating parameters of go/no-go and stop-signal tasks. Main task materials are simple geometric figures (e.g, squares, circles). However, RIT is different from a mere repetition of existing go/no-go or stop-signal tasks in several important ways: (a) with ascending levels, RIT becomes more difficult by systematically varying RI

task parameters integrated into each game level (i.e., frequencies of no-go or stop trials, stop-signal latencies, and increased stimulus potency via set switching); (b) RIT guides participants to make individually-tailored progress toward their own levels of challenge (i.e., each level is repeated until high accuracy is reached); (c) RIT contains video-game features to maximize participant's motivation (e.g., engaging story and graphics, and display of record scores); and (d) RIT provides trial-by-trial performance feedback to help participants make conscious efforts to improve their ongoing performance. In each 45-min session, five 7-min game levels are offered with brief inter-level breaks. After completing each level, a result page will summarize the participant's performance. The central training components of RIT are the same as those used in our pilot studies.

Similar to other cognitive retraining paradigms, the RIT is based on the rationale that repeated practice of the core cognitive process central to the condition would result in clinically meaningful improvement. The RIT is expected to allow individuals to practice (a) suppressing pre-potent stimulus-response association, (b) inhibiting potent ongoing response, (c) selectively inhibiting response to inappropriate stimuli, (d) exerting cognitive flexibility to changing targets, and (e) maintaining goal-directed responses in the given context. Based on the evidence suggesting RI as a core feature of OCD and our preliminary data, we predict that RIT will generate meaningful clinical improvement in OCD beyond a simple task practice effect which would improve only RI task performance without affecting OCD symptoms.

Similarly, PLT is a 30-level computer game but presents only go trials, and thus provides no opportunity to practice RI components (i.e., action withholding and cancellation). However, its 30-level structure and task stimuli are identical to those of the RIT program, and they also become increasingly difficult across level (by more abrupt onsets and increasingly shorter duration of the stimuli). We expect PLT to have negligible effects on RI capabilities and OCD symptoms. The RIT/PLT will be administered in a small therapy room at the UWM Psychology Clinic and Anxiety Lab. The participant will complete each training session following the computerized instructions. A trained administrator will be present in all sessions to assist in the event of any technical difficulties.

Primary and Other Outcome Measures

Considering the inclusion of two diagnostic conditions (OCD and TTM), we will obtain clinician-rated symptom ratings for both conditions, using the Yale-Brown Obsessive-Compulsive Scale and the NIMH TTM Symptom Severity Rating Scale. The primary outcome index will be a z-transformed score of the symptom ratings obtained from the two rating scales. We will also use the Clinical Global Impression (CGI) rating scale is a widely used brief assessment tool for evaluating illness severity, global improvement or change, and therapeutic response.

We will also use the stop-signal and go/no-go task, in which participants should promptly indicate the direction (left vs. right) of an arrow on each trial, but inhibit response when an auditory stop signal is presented. Stop Signal Reaction Time (SSRT; time taken to complete the inhibitory process) is estimated using the tracking algorithm, which adjusts the stop signal delay automatically (by 50ms) to maintain the rate of successful inhibition on stop-signal trials at 50%.¹⁰ This particular version has successfully demonstrated the RI deficits in both OCD patients and unaffected first-degree relatives.^{7,43} The SSRT is a behavioral RI outcome measure for this study. The go/no-go task asks participants to quickly press a button for letters (e.g., Q, P, T; go trials) except to the letter X (no-go trial).⁶⁷⁻⁶⁹ Twenty-five percent of the task constitutes no-go trials. The RI index from this task is the number of commission errors. Patients with OCD showed abnormal activity in fronto-striatal circuits while performing this type of go/no-go task.^{35,69}

STATISTICAL ANALYSIS PLAN

Power Analysis. We conducted power analyses using a conventional large effect size ($f = .40$). With $\alpha = .05$, a correlation of .5 among repeated measures, and a nonsphericity correction of .6, the required sample size is 9 per group to achieve the power of .80 in detecting a large group X time interaction effect ($f = .40$). Based on the recommendation from Ukoumunne et al.⁷⁰ that allows standard power analyses to be used for

multilevel models by multiplying the sample size by the design effect, the necessary sample size is 20 after an adjustment by a factor of 1.1, which was derived from an assumed intraclass correlation of .05. Taking into account 25% patient attrition ($n=5$), a total of 25 would offer an adequate sample size to detect a medium to large effect size. Thus, this proposal ($N=30$) is sufficiently powered ($=.90$) to detect a large effect, but is underpowered ($=.50$) to detect a medium effect ($f=.25$).

Specific Aim 1 - To determine the effectiveness of RIT in enhancing RI among OCD/TTM patients. To attain the objective of Aim 1, we will test the working hypothesis that RIT will show greater improvement in RI performance than PLT. Our primary analytic strategy is multilevel modeling, which effectively handles multi-session data with hierarchical structure (i.e., three time points nested in individuals), missing data, and serial correlation. To test the hypothesis, the level-1 intercept will be regressed on training condition to examine group differences, and the slope for time will be regressed on training condition to produce a cross-level interaction to examine the differential rate of change in RI performance between the two groups.

Specific Aim 2 - To determine the utility of the RIT in reducing OCD/TTM symptoms. To attain this objective, we will test the working hypothesis that RIT will show a greater reduction in OCD/TTM symptoms than PLT. Our primary analytic strategy is random effects mixed model analyses, in which the level-1 intercept will be regressed on training condition to examine group differences and the slope for time will be regressed on training condition to produce a cross-level interaction that examines group differences in the rate of change in OCD/TTM symptom z-scores.