Study Protocol

Study Title:

A Randomized Controlled Trial of Cognitive Control Training for Urgency in a Naturalistic Clinical Setting

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Overall Protocol Summary:

BACKGROUND AND SIGNIFICANCE

What do depression, binge eating, self-injury, addiction, anxiety, and aggressive behavior all have in common? These phenotypically diverse diagnoses and behaviors have each been associated with elevated impulsivity. More specifically, they are all linked with one particular type of impulsivity—urgency, which describes reflexive behavioral responses in response to either negative or positive emotions (12, 27). Cross-sectional studies have provided consistent support for the idea that urgency is a transdiagnostic construct (28), with a large meta-analysis showing robust correlations between urgency and symptoms of depression, anxiety, eating disorders, substance use, aggression, and borderline personality disorder (13).

Urgency is associated with destructive, maladaptive behaviors that are common across types of mental illness. For example, urgency is robustly correlated with measures of aggression (13, 29, 30). Urgency is also strongly correlated with non-suicidal self-injury (NSSI) and with suicide attempts (13, 31), and there is evidence that NSSI mediates the relationship between urgency and attempting suicide (32). Many studies have found strong relationships between urgency and alcohol and cigarette use (33, 34) and drug use (35, 36). Beyond these cross-sectional findings, urgency prospectively predicts maladaptive behaviors and symptoms over time, suggesting that this form of impulsivity is not merely an artifact of other symptoms. Urgency predicts the first occurrence of NSSI (16), as well as increased urges to self-injure in the context of sad mood (37). Urgency also prospectively predicts increases in drug and alcohol use, as well as problems related to using alcohol (14, 35, 38). Other prospective studies find that urgency is predictive of a range of destructive behaviors, such as problem gambling (15), risky sexual behavior (38), and binge eating (15). Given its role in a wide range of maladaptive behaviors, urgency is an important transdiagnostic treatment target, yet few studies have evaluated whether this aspect of impulsivity is responsive to existing treatments. In one recent study, urgency at baseline was associated with worse treatment outcome for people with binge eating disorder (39). To assess how urgency responds to treatment of acute symptoms of psychopathology, the PI conducted a Preliminary Study (A) analyzing change in urgency in 348 patients seeking treatment in a partial hospitalization program. Results of this study showed that although urgency decreased following treatment, negative urgency levels on discharge day from the program correlated with depression (partial $r = .37$, $p < .001$) and modestly correlated with NSSI urges (partial $r = .17$, $p < .01$) and urges to use substances (partial $r = .18$, $p < .01$). Together, these findings suggest that individuals with higher levels of urgency may not respond to existing treatments, and individuals for whom existing treatment does not adequately improve urgency continue to struggle with associated clinical symptoms.

In contrast to the paucity of treatment studies, many studies have evaluated the putative underlying mechanisms of urgency. These studies are largely based on the hypothesis that deficits in top-down cognitive control play a role in the expression of urgency (40). Although a number of candidate cognitive mechanisms have been tested, the most consistent evidence shows that deficits in prepotent response inhibition—the ability to override or cancel a dominant response—are most robustly correlated with urgency (1, 17). In a metaanalysis co-authored by this PI, findings showed that correlations between inhibition deficits and urgency were strongest in clinical samples (1). In addition to inhibition deficits, two-mode models of impulsivity and addiction emphasize the potential moderating role of working memory deficits,

which are hypothesized to exacerbate weaknesses in bottom-up reactivity to emotion (41). There is evidence that this theory applies to urgency as well, with one study finding that working memory deficits moderate the effect of inhibition deficits on negative urgency (18). In sum, both response inhibition and working memory may be crucial mechanisms underlying the expression of urgency.

Although most studies of mechanisms related to urgency have relied upon performance on behavioral tasks, studies have increasingly sought to understand links between cognitive control and urgency at the neural level. However, findings from these studies have not been consistent. Supporting the hypothesis that urgency is driven by weaknesses in top-down cognitive control mechanisms, some evidence shows that in the context of viewing emotionally stimulating pictures, negative urgency is related to lower activation in areas including the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (42). Other studies using functional connectivity analysis identify that higher levels of positive urgency are related to reduced connectivity between the ACC and areas of the parietal cortex (20, 30). In contrast, several studies suggest that during response inhibition tasks with negatively valenced images, urgency is related to increased activity in brain regions associated with cognitive control, including ventrolateral prefrontal cortex (vlPFC) and OFC (21, 43). Thus, it is not clear whether urgency is sustained by a deficit in the ability to recruit cognitive control regions or whether it is related to a maladaptive overuse of cognitive control to regulate behavior when experiencing negative affect, as has been suggested by Chester and colleagues (21). From either perspective, enhancing inhibitory control may help reduce urgency either by potentiating greater use of cognitive control or by providing training in the flexible application of control when necessary.

Existing research on the neural basis of urgency has yielded mixed results and has primarily used fMRI methodology. Surprisingly, very few studies have taken advantage of event-related potential ERP methods to examine neural correlates of urgency. ERP methodology is very well-suited to testing hypotheses about cognitive control, given its high temporal precision and the strong evidence for specific event-related potentials that relate to activation in brain regions implicated in cognitive control (e.g., [22, 23]). Only one study to date has used ERP paradigms in relation to urgency. In that study, urgency was unrelated to ERN amplitude unless individuals also reported low levels of conscientiousness; these individuals showed enhanced ERN amplitude in responses to errors (25). To our knowledge, there have been no investigations of the relationship between urgency and cognitive control using EEG methodology in a clinical sample.

Although the neural basis of urgency is not well understood, response inhibition and working memory are each well-characterized at the biological level of analysis. Evidence from lesion studies, fMRI, and EEG all suggest that inhibition is primarily based on activation of the right vlPFC, driven by activation in the right inferior frontal cortex (44, 45). In many common response inhibition paradigms, this activation is preceded by activation of the ACC, which is thought to detect conflict and potentiate the activation of inhibitory mechanisms (22). The neural basis of working memory is similarly well-understood, with strong evidence showing a central role for activation in the dorsolateral prefrontal cortex (dlPFC; 46). Beyond understanding the neural basis of these cognitive capabilities, research has increasingly shown the potential for cognitive training to induce improved performance on working memory and response inhibition tasks, as well as changes in the underlying biology supporting both of these cognitive functions. Several studies have shown training-based behavioral enhancements in inhibitory control, nearly all of which using either the Go/NoGo or Stop Signal paradigms (47). Multiple studies have now shown changes in brain activity associated with inhibitory control following use of these training paradigms (47). Many of these studies find evidence for reduced activation in regions of the

brain implicated in inhibitory control after training (47, 48), including reductions in the N2 event-related potential (ERP) thought to indicate preparation for inhibition (26). One interpretation of these findings, proposed by Spierer and others (47), is that training inhibition improves efficiency. Similarly, training using working memory paradigms has shown to be effective in increasing performance on working memory tasks, although these paradigms have been associated with increased activation of the dlPFC (49). In sum, these studies support the malleability of cognitive control at both the behavioral and neural level.

Many types of emotion regulation are supported by the same prefrontal cortical circuitry that subserves inhibitory control and working memory, including vlPFC and dlPFC (44, 50). Building on this shared basis, studies have found that training on cognitive control tasks leads to improvements in aspects of emotion regulation. For example, several studies using an adaptive auditory working memory task found reductions in rumination on negative affect following training (51, 52). Another recent study reported that inhibition training transferred to improved emotion regulation at the neural level on a reappraisal task after training (53). Thus, there is encouraging evidence that training on "cold" cognitive tasks (those that train basic cognitive abilities) may strengthen underlying neural circuitry important for regulation of "hot" cognition (regulation of affect). Based on the hypothesis of combined deficits in response inhibition and working memory influencing urgency, on evidence suggesting the malleability of inhibition and working memory, and on the potential for cognitive training to influence affective outcome, the PI of this proposal conducted a Preliminary Study (B) that tested a combined cognitive training intervention for urgency. In this study, individuals with high levels of urgency completed a six-session cognitive training intervention with a response inhibition task (adaptive Go/NoGo) and a working memory task (adaptive Paced Auditory Serial Addition Task [PASAT]). Three primary findings emerged, all of which directly inform the present study: (1) performance on response inhibition and working memory tasks improved from pre to post-training; (2) urgency showed a significant decrease from preto post-training (Cohen's d= 0.66), with no significant change during a waitlist control period, and (3) participants reported improvements on two measures of emotion regulation, including increased use of reappraisal (d = 0.52) and decreased rumination (d = 0.49). Despite these highly encouraging findings, this was a pilot study with several limitations, including lack of measurement of neural correlates of cognitive control, which prevents a clear conclusion about effects of the training on underlying cognitive control capabilities. Additionally, this study was conducted in a non-clinical sample of students and community members. Given that the relationship between inhibition deficits and urgency is strongest in clinical samples (1), it is unknown whether the intervention tested in this study might yield similar effects in a clinical sample.

SPECIFIC AIMS

1. The first aim of this study is to confirm target engagement of cognitive control training at both the behavioral and neural levels of analysis in a clinical sample of patients reporting high levels of urgency. We predict that compared to the control group, patients completing cognitive training will show lower interference (improved behavioral performance) and decreased ERN and N2 amplitudes on a Stop-Signal response inhibition task.
2. The second aim is to examine clinical outcomes of cognitive control training. Based on Preliminary Study A, we predict that all patients receiving treatment at the BHP will report lower urgency scores at discharge; however, we predict that this decrease will be significantly greater in those receiving cognitive training. In addition, we predict that

participation in the training will be associated with greater reductions in depression symptoms, urges to engage in NSSI, and craving related to substance use.

3. The third aim is to assess this training's feasibility and acceptability to patients in a real-world clinical setting. We predict that at least 75% of enrolled patients will complete all training sessions.

SUBJECT SELECTION

This is a sub-study under the existing protocol entitled "Establishing the Effectiveness of Cognitive-Behavioral Partial Hospitalization for Anxiety, Depression, and Overall Functioning" (# 2010-P-001047/6). We will recruit 110 participants from the patient population at the McLean Hospital Behavioral Health Partial Hospital Program (BHP). Inclusion criteria include: (a) BHP patient, (b) score above a 3 on either the UPPS Negative Urgency Scale or the UPPS Positive Urgency Scale at admission, (c) able to complete a computer task for 15 minutes, and (d) consent to main BHP study protocol (# 2010-P-001047). Participants will be excluded from participation if they are experiencing acute symptoms of mania or psychosis; if they are currently undergoing ECT; or if they have a history of a traumatic brain injury. Participants who are left-handed will be excluded from the EEG portion of the study but will be allowed to complete all other portions of the study.

Additional inclusion criteria for the research study will be consistent with admission criteria for the BHP program. Specifically, patients who are acutely psychotic and are deemed unfit for admission at the BHP will not be invited to participate in this study.

SUBJECT ENROLLMENT

Procedures under existing BHP protocol: Upon arrival to the Behavioral Health Partial Program, all patients will be oriented by the Community Residence Counselors and/or Nurse Practitioner (all CITI certified staff members) to the program, building and set-up of the treatment. Once oriented, patients will also be informed that as part of their treatment at the BHP they will be completing extensive self-report measures and a diagnostic interview. The research coordinator will explain to patients about our current research study examining the efficacy of CBT in naturalistic settings and asked whether or not they would like to consent to having their assessments be de-identified and included in our research database. It will also be explicitly instructed to patients, that if they were to refuse consent/participation, their treatment at the BHP will not be affected in any way. Patients will have the option to rescind their consent/participation at any point, and subsequently the Research Coordinator will take the appropriate measures to accommodate this decision.
Procedures under proposed protocol: The research coordinator or another member of the study staff will approach eligible patients (scoring above a 3 on either the Negative or Positive Urgency scale of the UPPS-P and consented to main BHP study) on their second or third day in the program and inform them about the study. Interested patients will then receive a detailed description of the study procedures, risk, and benefits and will sign an informed consent form.

Once enrolled, participants will be randomly assigned by a random number generator to one of two arms: treatment as usual + Cognitive Control Training (TAU+CCT), or treatment as usual (TAU). The PI or post-doctoral fellow will be responsible for randomization, and will notify the

Research Coordinator of each participant's assignment. Up to 20 participants will be assigned to the non-randomized pilot phase that will only include TAU+CCT, with no EEG session.

STUDY PROCEDURES

Design overview. We will conduct a randomized controlled trial of computerized cognitive control training among patients admitted to the BHP who report elevated scores on the urgency scales. Prior to beginning the randomized phase, we will enroll up to 20 participants into a pilot phase that will include the training program and all measure described below, with the exception of the EEG task. Next, Up to 90 patients will be randomized, with the goal of at least 68 patients completing baseline and discharge measures of impulsivity, symptoms, and craving for substances; half of these participants will be randomized to active training while half will undergo treatment as usual in the BHP. Participants randomized to the active training condition will be asked to complete eight to ten sessions of computerized cognitive training that combines working memory training and response inhibition training. This is a sub-study under the existing protocol entitled "Establishing the Effectiveness of Cognitive-Behavioral Partial Hospitalization for Anxiety, Depression, and Overall Functioning" (# 2010-P-001047/6). Data obtained under the existing BHP protocol will be shared with Investigators from this study.

Procedures under existing BHP protocol: This research will be conducted with each patient who enters our program (up to 900 adult patients each year). As the Behavioral Health Partial Program is an adult CBT-based program, all patients are at least 18 years of age and up. Upon registration in our program, patients will receive the Mini-International Neuropsychiatric Interview (M.I.N.I.), a 20-45 minute non-invasive, structured diagnostic psychiatric interview to assess for psychiatric diagnostic criteria. Patients will also be asked to complete a self-report questionnaire assessing for demographic variables, symptom severity, functional impairment, and CBT skill acquisition upon registration, upon discharge, and four and eight weeks following discharge from our program. Information will be stored on-site, in a locked drawer, in a secure office. Patients' original questionnaires will be maintained for no longer than five years. Only the Principal Investigator, Research Coordinator, Post-Doctoral Fellow, Nurse Director (Lynn Kopeski), and Program Director (Throstur Bjorgvinsson) will have access to PHI. However, the majority of PHI will be stored electronically. The proposed research will be using RedCap Database, an encrypted, electronic database that is both HIPPA compliant (Health Insurance Portability and Accountability Act) and approved by Partners IRB for the administration and storage of human subject information (for addition information on the RedCap Database feature see http://rc.partners.org). To minimize inconvenience and provide maximum benefit to patients, data collection will be streamlined as a part of standard clinical care. Clinically salient information, including diagnostic output and patient's self report scores, will be highlighted and presented to clinical team managers and others involved in patient services. Non-BHPP patients will not be able to participate in this research. Procedures for Proposed Protocol: Participants' data collected as part of protocol (# 2010-P-001047/6) will be used to characterize the demographic and clinical characteristics of the sample and as outcome assessments. Thus, only participants who consent to the main BHP study protocol will be eligible for the current study.

Baseline and Post-Training Research Assessment. All participants will complete a baseline assessment of symptoms, craving for substances, and cognitive control. Participants deemed eligible for the EEG portion of the study will complete one additional session on the day of the baseline assessment and one additional session on the day of the post-training assessment, which

will include high-density ERP data during completion of one of these cognitive tasks. Baseline assessments will take place on the day following admission or on the following day (3rd day). The tasks at baseline and post-training will include:

Self-Report and Interview Measures

a. Negative and Positive Urgency Scales are subscales of the UPPS-P, a multidimensional impulsivity self- report measure (56, 27). These scales reflect impulsive response to negative and positive emotions, respectively. The Negative and Positive Urgency scales are often highly correlated, and factor analysis has found that these dimensions share a common underlying construct of emotion-related impulsivity (57).

b. Alexian Brothers Urge to Self-Injure Scale (ABUSI; 60) is a brief self-report measure that assesses frequency and intensity of urges to engage in NSSI.

c. Craving Scale (based on [61]) is a 3-item scale predictive of future substance use for substances such as alcohol, opioids, and cocaine (61-63). Patients will rate their craving for their primary substance of choice.

d. Positive and Negative Affect Scale-10 item (PANAS-10; 69), a ten-item questionnaire assessing current positive and negative emotions. This scale will also be administered at the beginning of each of the training sessions.

e. Distress Intolerance Index (DII; 70), a ten-item self-report measure assessing perceived ability to tolerate distressing physical and emotional states.

f. Ruminative Responses Scale (RRS; 71), a self-report measure of thinking styles in response to negative mood.

g. Attentional Control Scale (ACS, 72); a brief self-report measure of cognitive control.

h. Edinburgh Handedness Inventory-Short Form (74). At the baseline session only, participants will complete a 4-item measure to determine handedness.

i. Debriefing. At the post-training session only, participants will complete a debriefing questionnaire to assess their perceptions of the study.

Participants will also complete two measures that are already administered as part of standard clinical care at the BHP:

The Mini International Neuropsychiatric Interview (MINI; 58) is a structured interview that assesses the presence of DSM-5 disorders. The BHP has well-established training and reliability procedures, including review of randomly-selected recorded MINI interviews to verify inter-rater reliability across the team. The MINI will be administered by doctoral practicum students and interns in clinical psychology who will receive weekly supervision by the post-doctoral fellow.

The Patient Health Questionnaire-9 Depression Scale (PHQ-9, 59) is a brief self-report measure of current depression symptoms.

Cognitive Control Tasks

a. Stop Signal Task (64) (with concurrent EEG/ERP for those completing the EEG session). Improvement in response inhibition will be assessed using a visual Stop Signal task, a well-established behavioral task that assesses ability to withhold a predominant behavioral response (65). Participants are presented with a series of stimuli on a computer (such as shapes) and are asked to respond as quickly as possible to the shape by pressing a corresponding button. On a minority of trials, a shape is followed by a "stop signal" cue, which signals participants to inhibit their response. The primary behavioral outcome is the Stop-Signal Reaction Time, calculated by subtracting the median interval between go and stop signals on stop trials from the median response time to the "go" trials (69). The Stop Signal Task will be used to evaluate transfer of response inhibition gains based

on the cognitive training intervention.

During completion of the Stop Signal task, EEG-eligible participants will undergo ERP recording using high-density, 96-channel electroencephalography (EEG, Brain Products GmbH). EEG recording will take place in specialized sound- and acoustically shielded testing room at the Center for Depression, Anxiety, and Stress Research (Director: Diego A. Pizzagalli, Ph.D.), located directly next to the BHP (approximately a 3-minute walk from door to door). EEG recording during the Stop-Signal task will be conducted to specifically identify two ERP components relevant to inhibition: the error-related negativity (ERN) and the N2. ERP data will be analyzed using BrainVision Analyzer software. ERN will be identified by a negative deflection of the ERP occurring within 100ms of errors committed on the Stop Signal Task (e.g., pressing the "go" button after a stop signal has been presented or incorrect responses). The N2 will be identified as the largest peak of a negative-going deflection occurring between 200 and 400 ms after stimulus onset on each trial, reflecting preparation for inhibition.
b. Dual N-Back Working Memory Task (67). To assess change in working memory, participants will complete a dual N-back working memory task. This task evaluates participants' ability to simultaneously remember both visual and auditory cues at varying time intervals. The Dual N-back task will be used to evaluate transfer of working memory gains based on the cognitive training intervention.
c. Trails Task (73). To assess baseline performance and change in processing speed and switching, participants will complete a brief computerized Trails Task. The Trails task will be used to evaluate how baseline speed and switching ability predicts response to training, and to evaluate potential transfer effects. This task is administered via TestMyBrain, which is a not-for-profit website dedicated to internet-based experiments. TestMyBrain uses SSL (secure sockets layer) encryption to protect any information that is being transferred between a browser and server. Data is backed up automatically on a nightly basis and only authorized users have access to the database. TestMyBrain does not collect any identifying information about the participant. All participant test data are transmitted directly from the TestMyBrain.org database to the Researcher using either secure http file transfer or secure SQL connection protocol.

Cognitive Control Training.
Participants randomized to complete the cognitive control training exercises will complete 8 to 10 sessions of the exercises described below, lasting about 15 minutes each time. Prior to each training session, participants will view a brief powerpoint slide reminding them how the task pertains to impulsivity. Participants will be asked to complete ten sessions; however, participants may complete as few as five sessions if there are problems finding time to schedule all ten sessions (e.g., computer availability, participant availability during lunchtime or before or after program hours, etc.). The two training tasks will alternate on each day of training: each day of training, participants will complete either the Go/NoGo task or the PASAT task described below; participants will be randomly assigned to begin with either the Go/NoGo task or the PASAT task.

a. *Adaptive Go/NoGo* is a response inhibition training paradigm previously used by this PI to train inhibition (19) based on similar Go/NoGo training paradigms used in previous training studies (i.e., 48, 68). Participants are instructed to press a button as fast as possible ("go") whenever they see a stimulus (a single letter) presented onscreen; however, on each new block they must withhold their response when a target letter is presented ("no-go"), with the target letter switching in each new block. The training includes three 5-minute blocks per session. Similar to other inhibition training paradigms (46), the difficulty level is adapted to performance

based on participants' reaction time to "go" trials; as participants correctly respond to "go" trials, the amount of time in which they have to respond to these trials is reduced. The nonadaptive version of this task will be used to assess baseline and post-training task performance.
b. *Adaptive Paced Auditory Serial Addition Task* (PASAT, [51]) In this task, participants listen to a series of aurally-presented numbers and are instructed to add each number to the last number presented and enter the sum onscreen. The performance-adaptive version of the task decreases the inter-stimulus interval as performance improves (making the task more challenging by reducing the amount of time per trial, or decreasing difficulty by increasing time). The training includes three 5-minute blocks per session. The nonadaptive version of this task will be used to assess baseline and post-training task performance.

Sessions will be completed during the lunch hour, in between groups, or at the end of the day. Sessions will begin on the second or third day and continue until discharge. The average length of stay in the BHPP is 8.5 days. Sessions will be completed in the BHP computer lab, where patients complete daily progress monitoring as part of their standard clinical care, or a private room when available. A member of the study staff, typically the research coordinator, will set up the computer task and be available for any questions or problems.

BIOSTATISTICAL ANALYSIS: ERP data will be pre-processed to remove artifacts (e.g., by using independent component analyses) and identify ERPs using BrainVision Analyzer. Hypothesis 1 will be tested using a 2 (condition: TAU+training, TAU) x 2 (time: baseline, discharge) mixed-model analysis of variance (ANOVA) with Stop-Signal Reaction Time as the dependent variable; two separate ANOVAs with the same predictors will also test dependent variables of ERN and N2 amplitudes. Hypothesis 2-3 will be similarly tested via mixed-model ANOVA with the same predictors; one model will test the DV of Negative Urgency; one will test the model of Positive Urgency; and three models will test change in craving, depression, and self-harm urges. Hypothesis 4 will be tested via descriptive statistics assessing the percentage of enrolled participants who complete the training intervention and their mean level of satisfaction at discharge. Analyses will consider the impact of several a priori potential confounds on effects of the intervention, using Pearson correlations to test if performance on cognitive tasks are related to age, medication, primary diagnosis, or percentage of completed training sessions. If significant correlations are identified, these variables will be included in the above analyses as covariates.

Power analysis: A priori power analysis conducted in G*Power indicated that a sample size of 68 individuals is necessary to achieve adequate power (1- β= 0.9) to detect small to medium effects (Cohen's f = 0.2) in repeated-measures ANOVA. To ensure adequate power, we will recruit up to 90 patients to begin the study, based on predicted attrition rates (see "Potential Problems and Alternate Strategies"). To complete recruitment within two years, we will enroll 3.75 patients per month, or roughly one per week. In previous cognitive training studies conducted by Dr. Beard in the BHP, she has successfully enrolled patients at a rate of one per week, indicating that the target in the present study is highly feasible.

RISKS AND DISCOMFORTS

Potential Risks
i. Privacy and Confidentiality of Data: As with all research, there is a risk of loss of confidentiality and/or breach of data security. Given the substantial measures put in place to protect privacy and confidentiality within the BHP's clinical research program (described

above), there is a low likelihood of this risk.
ii. Frustration: The behavioral tasks that are administered at the baseline, training sessions, and discharge session require sustained concentration and focus. These tasks are relatively demanding by design, and thus some participants may feel moderately frustrated by the challenging nature of the tasks. However, in order to appropriately engage the putative underlying mechanisms of response inhibition and working memory capacity, it is necessary to include tasks that assess participants' ability to effectively recruit these domains under somewhat challenging conditions. Thus, there is a moderate possibility of frustration after completion of these tasks for some individuals.
iii. Fatigue: Participants may become tired following completion of relatively demanding cognitive tasks that require sustained concentration and focus. This may be particularly true for participants randomized to the TAU+training condition, as this condition involves up to 10 sessions of 15-minute cognitive exercises. It is likely that some participants may feel mentally fatigued after completion of such training sessions.
iv. Emotional Discomfort: Participants may find it upsetting to answer questions on self-report measures about their level of depression symptoms, urges to engage in self-injury, and/or craving for substances of abuse. However, these questions do not greatly differ from questions that are asked as part of routine clinical care in the BHP, and thus the risk of increased discomfort is relatively low.
v. Worsening of Clinical Symptoms: Given the acute symptom presentation of this proposed study sample, it is possible that some participants may report new or worsening clinical symptoms during the course of the study, such as suicidal ideation or increased depression. As this study is conducted in a naturalistic setting, participants recruited for this study are expected to vary substantially in their clinical presentation and course of treatment, and thus there is a moderate risk of worsening clinical symptoms.
vi. Discomfort with electrodes during EEG recording: Application of the net of EEG sensors to the scalp may feel mildly uncomfortable. We foresee only minimal risks from the EEG recording, a commonly and widespread procedure used to non-invasively measure electrical brain activity. The EEG will be recorded with actiCAP active electrodes (Brain Products GmbH), which requires no scalp abrasion. On rare occasions, individuals with very sensitive skin may experience a slight irritation at the site of sensor application due to the use of electrolyte gel. The Brain Products actiCHamp/actiCAP EEG system has been certified as safe under the safety and effectiveness standards of medical electrical equipment published by the International Electrotechnical Commission (IEC 60601-1:2005, 3rd edition).

b. Protections Against Risk
i. Privacy and Confidentiality: To protect participants' privacy and confidentiality, multiple protective measures will be implemented. Identifying data (participants' names) will be stored separately from all other study documents. A key database linking participants' study ID numbers and their names will be stored on a secure, protected server that is separate from all other study documents. Participants' original informed consent documents are stored in a locked file cabinet in a locked office accessible only by senior members of study staff. All study data will be stored electronically in protected databases, stored on a McLean Hospital research server accessible only to members of study staff. We plan to make de-identified data from this study available via the NIMH Data Archive (NDA) in accordance with NIMH policy, to be stored in the National Database of Clinical Trials. Apart from the self-report and interview measures that are also used in clinical care, all other study measures and tasks will be completed in private clinic rooms to maintain confidentiality within the program.
ii. Frustration and Fatigue: Participants will be fully informed that some of the cognitive tasks

may induce frustration and/or fatigue. To mitigate these risks, participants will be encouraged to frequently take breaks during completion of the training tasks. The cognitive training sessions also have built-in task-adaptive programming that automatically adjusts task difficulty based on participants' online performance. This means that for participants whose score begins to decline due to either frustration or fatigue, the task will automatically slow down in order to become moderately easier to complete. In addition, a member of study staff will be physically present during completion of all cognitive tasks and will be trained to monitor participants for signs of increased fatigue or frustration. These members of study staff will encourage participants to take breaks between blocks of the task.

iii. Emotional Discomfort: Participants will be reminded that they may discontinue a questionnaire or interview at any time if they feel uncomfortable or upset answering questions. Participants will also be encouraged to share any emotional distress with a member of study staff, so that study staff can appropriately refer that participant to speak with a professional clinical member of their treatment team (e.g., case manager, psychiatrist, or therapist). In addition, the study sponsor (Dr. Courtney Beard) and the BHP Director (Dr. Throstur Bjorgvinsson) are licensed clinical psychologists who are available during program hours to provide clinical assessment of study participants, if necessary.

iv. Worsening Clinical Symptoms: Members of study staff will be trained to monitor and recognize signs of increased distress among study participants. As part of routine clinical care in the BHP, certain self-report measures that are part of the main study protocol (# 2010-P-001047/6) are reviewed on the day they are completed; if answers to self-report questions indicate a heightened level of risk for self-injury or suicidality (e.g., increased suicidal ideation or urges to self-harm) a staff member will contact a member of the patients' clinical team. Similarly, clinicians who administer the interview-based measure of symptoms and diagnoses will assess for suicidal ideation and report any significant findings to other clinical team members.

v. EEG session: Collecting EEG data is a common and widespread procedure used measure to assess electrical brain activity on the surface of the head. The only known risk is that on rare occasions, individuals with very sensitive skin may experience a slight irritation at the site of sensor application due to the pressure from the blunted end of the needle that is used to ensure a good connection between the scalp and the electrode. The EEG cap may become uncomfortable after a long exam, but we will do our best to adjust it so this will not happen. Study staff will undergo extensive training and practice with EEG procedures prior to collecting EEG data with human subjects, and study staff will be trained to routinely check in with participants to make sure they are still comfortable with EEG procedures.

POTENTIAL BENEFITS

All participants who enroll in the study receive additional interactions with members of study staff, which may benefit participants by providing them with enhanced symptom monitoring while attending the partial hospital program. If participants show evidence of worsening symptoms, members of study staff are trained to immediately refer that person to their clinical team, which may enhance their existing clinical care. Finally, participants who are enrolled in the TAU+training condition receive access to an experimental cognitive training program that might help to reduce impulsivity.

Although this study also involves the risk of fatigue, frustration, and possible emotional distress while filling out questionnaires, these risk factors are common in studies of cognitive training in clinical samples. Previous studies using similar designs have yielded important conclusions about the utility of cognitive training paradigms among people with mental illness, while also carrying similar risks. We believe that the potential benefit of testing cognitive training in this setting outweighs the slight to moderate risks associated with this type of study design. Similarly, although the risk of breach of confidentiality is a significant concern for all research, we believe that the protections described above are adequate and that the benefit of novel treatment development is an important goal that partially offsets these risks. The proposed research also has broader potential benefits outside of the immediate study participants. The results of this study may well provide important conclusions about the extent to which cognitive training paradigms for impulsivity can be integrated into the partial hospital context, which may benefit future generations of partial hospital patients who struggle with similar forms of impulsivity.

MONITORING AND QUALITY ASSURANCE

The proposed research plan will strictly adhere to the data and safety monitoring guidelines set forth by McLean Hospital and Partners Healthcare. As the proposed study is a relatively small clinical trial that does not meet the definition of an NIH-defined Phase III clinical trial, and given the relatively low risk to study participants, we have not proposed a full Data Safety and Monitoring Board for the present study. However, we will implement a series of data and safety monitoring procedures to ensure optimal safety for all participants. The Principal Investigator (Andrew Peckham) and the study sponsor (Courtney Beard) will hold responsibility for monitoring the safety of study participants and the security of data collected in this study.

Safety monitoring will be conducted on an ongoing basis via several procedures. First, participants' self-report measures include data that indexes patient safety (i.e., suicidal ideation, self-harm urges), and these measures will be reviewed daily by a member of study staff. If participants report an increase in risk based on these measures, the study staff member will immediately contact the PI. Also, members of study staff will inform the PI of any participants who verbally report any new safety concerns (either during the clinical interview or during routine study procedures). Any adverse events or serious adverse events will be reported to the Partners Healthcare Institutional Review Board (IRB). In accordance with Partners Healthcare policy, any unanticipated problems or adverse events will be reported within 5 working days or 7 calendar days from the date the problem is discovered. Serious adverse events would be reported within 24 hours of discovery.

In addition to these ongoing safety procedures, the PI will conduct a review of specific data points relevant to patient safety every twelve months. This review will encompass a statistical test of changes in symptoms on self-report measures from baseline to discharge in both

the TAU and the TAU+training groups. This will allow for evaluation of any potential negative effects arising from participation in the training program.

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