Medication-assisted psychotherapy: Using ketamine-enhanced RODBT to target neural and behavioral mechanisms of action in emerging adults with moderate to severe depression

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A Introduction

A1 Study Abstract

Heightened performance monitoring and overcontrol (HPM/OC) is a transdiagnostic phenotype characterized by checking behaviors, cognitive inflexibility/rigidity, and social concern/perfectionism and underlies treatment resistant depression (TRD). TRD presents a sizeable public health concern with higher hospitalizations, suicide, disability and mortality rates compared to major depression, and $44 billion yearly in societal cost. The goal of this project is to examine feasibility and efficacy of a cutting-edge medication-assisted psychotherapy, ketamine-enhanced Radically Open Dialectical Behavior Therapy (RODBT) in 15 emerging adults with moderate to severe depression. We aim to test whether ketamine-enhanced RODBT targets the purported mechanism of action, HPM/OC. RODBT alone has not enacted neural change and ketamine may prove as a catalyst to treatment-response. Given the current mental health crisis, only exacerbated by COVID-19, synergistically targeting TRD with fast-acting (ketamine) and durable (RODBT) mechanistic treatment, early in the developmental course, is imperative in lessoning the lifelong burden of psychiatric illness.

A2 Primary Hypothesis

Aim 1: Examine preliminary feasibility and efficacy of ketamine-enhanced RODBT. Hypothesis 1a: Ketamine infusions 1-2 days prior to RODBT psychotherapy sessions will be well-tolerated and feasible. Hypothesis 1b: Using individual session data, ketamine will catalyze psychiatric symptom change in RODBT and ketamine-enhanced RODBT will be associated with decreasing trajectories of depressive symptoms.

Aim 2: Examine preliminary efficacy of ketamine-enhanced RODBT in engaging neural and behavioral mechanistic targets in young adults with moderate to severe depression. Hypothesis 2a: Ketamine-enhanced RODBT will be associated with neural ERN reductions and neural RewP increases. Hypothesis 2b: Ketamine-enhanced RODBT will be associated with behavioral cognitive flexibility, openness, reward responding and social functioning improvements.

A3 Purpose of the Study Protocol

The current study will be the first to test ketamine-enhanced RODBT in young adults with TRD, providing preliminary evidence of a more potent, fast-acting *and* durable treatment for the intractable presentation of TRD by examining to how ketamine may enhance or catalyze response to RODBT. Moreover, medication-assisted psychotherapy is still in its infancy, and the current project will be the first to mechanistically target HPM/OC using ketamine, examining whether the combination of ketamine and ROBDT engage neural and behavioral mechanistic targets.

Additionally, taking both a deep-dive approach via individual session data as well as examining neural change across treatment will provide an encompassing methodological picture of how ketamine and RODBT synergistically impact outcomes. The combination of fast-acting ketamine with a psychosocial intervention shown to provide longer-term outcomes may lead to lessened severity, chronicity, impairment (and societal cost) across the lifespan for emerging adults with moderate to severe MDD and TRD.

B Background

B1 Prior Literature and Studies

Self-control is adaptive and protective against onset of multiple forms of psychopathology. (1) A lack of self-control, or undercontrol, has been widely studied and exhibits across multiple psychiatric disorders. However, perhaps equally important and far less understood is excessive control, or 'overcontrol'. Although adaptive to monitor one's performance to learn from mistakes, heightened performance monitoring is associated with checking, perfectionism, anxious apprehension and cognitive inflexibility/rigidity.(2,3,7,17) Heightened performance monitoring and overcontrol (HPM/OC) is evident across multiple treatment-resistant psychiatric disorders, including Treatment Resistant Depression (TRD). Major depressive disorder (MDD) is highly common and often treatable, but for the 30% who do not respond to treatment, an especially pernicious course of suffering, disability and mortality often ensues (3). Individuals with TRD have early onset, more psychiatric comorbidities, higher suicide rates and are twice as likely to be hospitalized than those with MDD (4,5).

The total annual cost associated with TRD in the US is an estimated $44 billion (47% of the financial burden of MDD) (6). In line with NIMH's focus on targeting mechansims in the treatment for psychiatric illness and given TRD is an intractable psychiatric presentation with a significant societal burden, there is a critical need to develop innovative and durable treatment modalities that directly target transdiagnostic mechanisms in TRD, such as HPM/OC.

Although psychotherapy has been neglected in TRD,(7) a novel psychotherapy, Radically Open Dialectical Behavior Therapy (RODBT) directly targets the underlying mechanism of HPM/OC evident in TRD.(1) Rather than targeting psychiatric symptoms, RO DBT targets underlying and transdiagnostic HPM/OC by focusing on decreasing rigid behavioral patterns, increasing receptivity and openness to new experiences and feedback, and increasing social connectedness.(8) RODBT demonstrates empirical support in TRD, including a recent multi-site RCT.(9,10) Recent findings, including those from the PI and prior CTRFP funding, demonstrate that RODBT not only decreases psychiatric symptoms, but also improves behavioral flexibility, reward responding and quality of life and decreases maladaptive behavioral HPM/OC.(11,12) Moreover, the PI has recently demonstrated that change in mechanistic processes relevant to HPM/OC (i.e., increasing flexibility and social functioning), is directly associated with decreased depressive symptoms in a large RCT for TRD.(13) This provides direct evidence that targeting core processes evident in HPM/OC is associated with psychiatric symptom change. Yet, in the only study testing neural mechanistic target engagement in RO DBT, the PI found no change in electroencephalogram (EEG) based neural indicators relevant to HPM/OC, one assessing heightened performance monitoring, the error-related negativity (ERN) and one assessing reward responding: the reward positivity (RewP).(12) Although preliminary evidence indicates RODBT can engage a behavioral mechanistic target, and this target engagement is associated with decreased psychiatric symptoms, neural change associated with RODBT has not yet been detected in treatment-resistant psychiatric presentations.

Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor(14) and has repeatedly shown to be a safe, tolerable,(15) and effective means of treating depression, in particular TRD.(16) The therapeutic mechanisms of ketamine are not fully understood; however, ketamine is associated with changes in synaptic function and neuroplasticity, and these changes are correlated with a decrease in depressive symptoms(17). It has been theorized that ketamine's effectiveness, is in part because it, "...promotes a time-out from ordinary, usual mind, relief from negativity, and an openness to the expansiveness of mind..." (p. 191).(18) Although anecdotal, ketamine may theoretically aid in in increasing openness and decreasing negative rigidity, core features of the HPM/OC phenotype and vital aspects of RODBT treatment. Ketamine's effects are fast-acting and transient, which has led to growing interest in combining ketamine with psychotherapy(17,18). Facilitating new neural connections make ketamine a powerful adjunct to existing therapy, and in particular might be amenable to

facilitating change in RODBT. Ketamine has demonstrated change in neural reward responding and has improved social functioning in depression,(18) both of which are central to the HPM/OC phenotype. Indeed, work from key personnel on this proposal demonstrate that in adults with TRD, ketamine infusions demonstrate response-dependent changes in functional connectivity in the anterior cingulate cortex (ACC), default mode network and limbic/reward structures, including the amygdala and nucleus accumbens.(19) Of note, the ACC has been repeatedly implicated in performance and error-monitoring (e.g., HPM/OC),(20) and is where the EEG-based neural marker, the ERN is thought to originate(21) while the nucleus accumbens is a reward structure where the RewP is theorized to originate from.(22) Together, ketamine may provide initial, fast-acting change to catalyze and facilitate longer-term neural and psychiatric change in RODBT in individuals with TRD. Ketamine-assisted psychotherapy is still in early stages of study,(18) so the current proposal will take a 'deep-dive' examination of feasibility and session-by-session change in ketamine- enhanced RODBT. This will allow us to a) test whether ketamine acts as a catalyst to RODBT, increasing openness and flexibility for RODBT therapy sessions and b) examine trajectories of change across the treatment, assessing when ketamine induced plasticity is associated with the largest drop in psychiatric symptoms (Aim 1). Additionally, repeated EEG neural assessments (baseline, post-ketamine and post-RODBT) will allow us to a) test whether a shorter course of RODBT, boosted with concurrent ketamine (8 weeks) is enough to enact neural change, or, whether the full course of ROBDT (16 weeks) is necessary to elicit neural change and b) assess whether targeting the neural and behavioral mechanism of HPM/OC is directly associated with improving MDD symptoms and functioning (Aim 2).

B2 Rationale for this Study

Given TRD is characterized by chronicity and high societal cost[6,7], effectively treating it early in its' course is imperative for lessening burden over the lifespan. TRD has earlier onset than treatment-responsive MDD, thus, persistent moderate to severe depression during emerging adulthood may be an early manifestation of TRD and a window of opportunity for early intervention.[4] Moreover, since the start of the COVID-19 pandemic, MDD rates have significantly increased, especially for individuals under age 40 and students.[23] Thus, given the current mental health crisis, targeting TRD with fast-acting *and* durable mechanistic treatment at the earliest developmental timepoint is imperative. The current research team brings together relevant expertise across adolescent/young adult (Gilbert, Nicol) and adult (Farber, Lenze) populations to conduct highly innovative medication-assisted psychotherapy research that could profoundly impact new lines of treatment research. The current project brings together this distinct expertise into a novel collaboration that we have reason to believe may synergistically lead to both fast-acting (ketamine) and also longer-

lasting (RODBT) mechanistic change in a highly treatment- resistant psychiatric presentation that demonstrates increased prevalence during the transition into adulthood.

C Study Objectives

C1 Primary Aim

Aim 1: Examine preliminary feasibility and efficacy of ketamine-enhanced RODBT. Hypothesis 1a: Ketamine infusions 6-24 hours prior to RODBT psychotherapy sessions will be well-tolerated and feasible. Hypothesis 1b: Using individual session data, ketamine will catalyze psychiatric symptom change in RODBT and ketamine-enhanced RODBT will be associated with decreasing trajectories of depressive symptoms.

C2 Secondary Aim

Aim 2: Examine preliminary efficacy of ketamine-enhanced RODBT in engaging neural and behavioral mechanistic targets in young adults with moderate to severe depression. Hypothesis 2a: Ketamine-enhanced RODBT will be associated with neural ERN reductions and neural RewP increases. Hypothesis 2b: Ketamine-enhanced RODBT will be associated with behavioral cognitive flexibility, openness, reward responding and social functioning improvements.

C3 Rationale for the Selection of Outcome Measures

The outcome measures of neural and behavioral HPM/OC and neural reward and social responding have been chosen to assess the purported underlying mechanisms of change contributing to symptom presentations. We also included functioning and psychiatric symptoms to assess whether targeting a mechanism also influences symptom presentation.

D Investigational Agent

D1 Dose Rationale and Risk/Benefits

Details of Infusion

To ensure dose accuracy, participants will have weight confirmed prior to each infusion. All female participants will complete a urine pregnancy test immediately prior to their first ketamine infusion and will be informed that it is not advised to have unprotected sex throughout the ketamine infusion period (1 month). After safety ratings (see table below) are performed, an IV line will be inserted into upper extremity by research personnel. The ketamine will be infused using an IV infusion pump at a rate of 0.5 mg/kg of body weight over 40 minutes. Heartrate, blood pressure, and pulse-oximetry will be routinely monitored throughout the infusion and for approximately up to two hours after the end of the infusion. Safety ratings will be repeated prior to discharge. After normalization of any psychotomimetic symptoms or blood pressure elevation and IV removal, participants will be discharged.

Direct physical or psychological risks are minimal in the administration of behavioral and electrophysiological measures. Individual psychosocial therapy sessions can elicit some psychological distress while group sessions can elicit some psychological distress or social anxiety. Behavioral tasks can lead to some concern of performance or frustration. Additionally, participants may become bored or tired during the experimental sessions. Some mild discomfort may be associated with the application of the miniature surface electrodes and when skin is mildly abraded. At no time will subjects be coerced to participate in any aspect of testing, subjects will be told that at any time they wish to terminate the experiment or therapy, they are free to do so. There is also always a risk of loss of confidentiality; although this risk is minimal given data are stored electronically behind Washington University's firewall. Lastly, there is a risk of time burden.

Risks of Ketamine infusion:

Likely	• Feeling light-headed, "high," exhilarated, and/or happy • Having perceptual changes or hallucinations, floating sensations • Difficulty concentrating, paying attention, or remembering as many items as usual from a list (like items on a grocery list). • Mild and temporary increases in blood pressure • Feeling nauseated.
Less Likely	• Feeling dizzy, sleepy, anxious, and suspicious.
Rare	• Feeling sad, scared, confused, and/or disoriented. • Moderate and temporary increases in blood pressure. • Future abuse of ketamine • Prolonged psychosis in individuals with a pre-

	existing psychiatric condition

Risks of Blood Draws:

The blood draw may cause bleeding bruising, or pain. Some people may become dizzy or feel faint. There is also a rare risk of infection.

Risks of an EKG:

After an EKG, participants may have mild irritation, slight redness, and itching at the places on their skin where the recording patches are placed.

Risks of Radically Open Dialectical Behavior Therapy:

Participants are informed that participation in this research is strictly voluntary, they are free to discontinue participation in the experimental session or psychosocial therapy at any time, and that information obtained is confidential. We will minimize discomforts and fatigues associated with the performance-based behavioral and EEG assessments by allowing participants to take breaks as needed. Participants will be encouraged to take breaks as frequently as desired and to discuss questions and concerns in any nature. Breaks will be offered during the EEG procedure. Experimenters will regularly ask adolescents and caregivers how they are feeling and remind them to ask questions or express any concerns that come to mind. Similarly, study therapists will conduct weekly check-in's with clinical trial participants regarding how they are feeling and if they have any questions or concerns about their treatment. Study therapists will assess if participant weight loss is occurring or psychiatric mental status is declining, and if so, they will be stepped up to a higher level of care.

Subject confidentiality will be assured through a multi-layered approach, entirely compliant with HIPAA regulations. First, all demographic and other identifying information will be stored under at least two locks/passwords (in a password protected document on a password protected computer in a locked office or in a locked cabinet in a locked office). The participants' name and study number will be stored in a master file that contains no other demographic or research information. This master file will be a password protected document and stored on a password-protected computer. All other non-identifying information will only be assigned an ID and will also be protected under two locks/passwords. Only Dr. Gilbert and designees will have access to this information. Under no circumstances will individually identifiable data be released to anyone without written consent of the subject. Any data analyses and publications from this study will not individually identify participants and will focus on grouped data. The research data (including clinical adolescent and caregiver-reported assessments) will be examined as it is collected to review any clinical implication of the information. If any incidental findings are uncovered or clinical attention warranted at any point during study participation, this will be immediately

discussed with the principal investigator (Dr. Gilbert), a licensed clinical psychologist, and this information and will be discussed with participants. Similarly, research study therapists will have weekly ongoing supervision and consultation meetings to discuss therapy cases. If increased clinical attention is warranted at any point during the four-month therapy, this will be immediately discussed with the PI and, if needed, the participant will be stepped up to a higher level of care.

Benefits:

The experimental research measures in this project will not directly benefit the participants, other than the knowledge that they are contributing to our understanding of the underlying factors that may cause treatment-resistance to previous treatments and may provide insight into a novel medication-enhanced psychotherapy and thus, there is a benefit of contribution to society. In the therapy portion of the project, it is also possible that participants may experience improved symptoms of depression, mood, anxiety, as well as reduced tendencies of HPM/OC. As part of the ketamine treatment, participants may also experience improved symptoms of depression and anxiety. There is a possible effect that the combination of ketamine and RO DBT will be especially beneficial in combination, although this is unknown, as it is a goal of the study to test the combined treatment. As mentioned above, measures are being taken to minimize any potential risks.

E Study Design

E1 Overview or Design Summary

Eligible patient (n=15) young adults will attend a baseline session where they will undergo an ERP neural assessment and fill out questionnaires. Then, participants will complete 4 weeks of ketamine and 4 months of RO DBT. Participants will start with 2 weeks of individual therapy (RODBT) to orient to therapy and infusion protocols. Then, participants will complete a 4-week course of twice weekly 40-minute ketamine infusions administered 6-24 hours prior to RO DBT psychotherapy (also when RO DBT group therapy will commence). Following completion of the 4-week ketamine-enhanced RO DBT, participants will complete another in-person session with an EEG and behaiovral assessment. Next, participants will continue to complete RO DBT treatment of individual and group treatment for an additional 16 weeks. At the end of this treatment, participants will complete a third session where they will undergo an ERP neural assessment and fill out questionnaires. Participants will also complete self-reported questionnaires following each ketamine and RO DBT

session (4 weeks) and weekly self-reported questionnaires during non-ketamine RO DBT.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Young adults with treatment-resistant depression: Inclusion criteria:

- Males and females aged 18-65
    - Moderate to severe persistent depression [treatment resistant depression – TRD] (exhibiting 2+ unipolar major depression episodes (non-delusional) with prior treatment non-response to antidepressant or psychosocial treatment
        - Treatment-resistant depression: defined as unipolar major depressive disorder, that persists despite ≥ 2 adequate antidepressant trials of different classes in the current episode; including at least one evidence-based second-line treatment in the current episode (including serotonin norepinephrine reuptake inhibitors, bupropion, tricyclics, monoamine oxidase inhibitors, or augmentation with an atypical antipsychotic, stimulant, bupropion, lithium, or Triiodothyroinine)
    - higher proportion of OC words endorsed compared to UC words on the Word Pairs Checklist
    - no current or past psychosis
    - English speaking
    - Able to attend in-person behavioral sessions and ketamine/therapy visits
    - Willingness to have RO DBT as only psychosocial treatment engaged in (medication treatment may continue—but see below for exclusion)

2.a Exclusion Criteria

Exclusion criteria:

- Outside age range
- Significant neurological condition (i.e., seizure, stroke, severe head injury) or mental retardation (IQ<70)
- Current or recent substance use disorder, actively suicidal or homicidal (e.g., requires hospitalization)
- Use of naltrexone, memantine or medication considered contraindicated with ketamine
- Baseline systolic BP > 150 systolic or 90 diastolic at evaluation. Participants who initially present with elevated blood pressure may be re-assessed; and if needed, referred to their healthcare provider for hypertension management

- Taking more than 2 adequately-dosed oral antidepressants
- Inability to understand, speak and read English sufficiently
- Not be pregnant or at risk of becoming pregnant
- Medical conditions or medication usage that in the judgement of the investigators puts the patient at unreasonable safety risk
- First degree relative with a psychotic diagnosis involving hallucinations, delusions, or disorganized thinking and speech (e.g. schizophrenia, schizoaffective disorder, etc)

2.b Ethical Considerations

Re: Thearpy and ketamine trial-- Participants are not randomized. They will be fully informed of the free therapy and ketamine trial and will not be coerced into it. Free therapy and ketamine will be provided to all patients (as this is a feasibility and acceptability study). If any patient participating in the study needs a higher level of care, they will immediately be removed from the treatment protocol and will be coordinated with other providers to ensure they get the care necessary. If any patient participating in the study decides they no longer want to be in the trial, they can end at any point and it will be coordinated to help them continue treatment with other providers.

Re: experimental session—all participation is voluntary, including answering questions and participating in the ERP.

2.c Subject Recruitment Plans and Consent Process

Study population:
Young adults age 18-65 years with TRD who exhibit HPM/OC.

Consent process: If an interested participant contacts the research team about the study, a member of the research team will provide information about the study and required elements of consent over the telephone (see attached "Consent for Phone Screen") prior to obtaining the participants verbal consent to participate in the screening elements of the study. This phone screen will allow possible participants to ask questions and clarifications prior to coming in person for the in-person consent process (and includes the child having the opportunity to ask questions). If a participant meets eligibility criteria for enrollment in the study based on their Initial Phone/Exclusion Screen and the participant indicates they wish to continue with the study, the participant will receive an email to complete the a measure of HPM/OC, the Word Pairs Checklist. The participant must consent to complete these questionnaires. If the participant is eligible following completion of the phone screen and questionnaires, the research team will notify the participant of their eligibility and ask whether they want to continue with the study. If the participant is unsure, the research assistant will provide

unlimited time for the participant to consider whether they would like to participate in the study and a research assistant will notify the participant they can contact the research team if they would like to potentially participate in the future (they may have to re-complete the phone screen at that future time). If the person is still interested, the research team will schedule an in-person session.

The consent process will take place in person at Washington University in St. Louis Department of Psychiatry in a private room with a research team member. The consent process will include providing ample time for the young adult to read/review the consent form. This consent will consents for the experimental sessions and the free ketamine and therapy portion. There is no randomization: if an potential patient participant is interested in the free ketamine/therapy, they can participate in that until we have 15 participants in the therapy portion. A trained research assistant will also discuss the procedures of the study and will answer any questions the participant may have prior to signing. Research team members will remind participants that their participation is completely voluntary and they can choose to withdraw at any time.

2.d Early Withdrawal of Subjects

Participants can withdraw at any point if they desire. Participants in need of higher levels of care will be withdrawn by the PI if medically/psychologically unstable or if they express active suicidal ideation.

2.e When and How to Withdraw Subjects

Participants in need of higher levels of care will be withdrawn by the PI at any point if medically/psychologically unstable or if they express active suicidal ideation and need to be hospitalized. If a participant desires to withdraw, as soon as they inform the study team, the team will remove the participant fro current and future study procedures.

2.f Data Collection and Follow-up for Withdrawn Subjects

Data will not be collected for withdrawn subjects once they withdraw. Follow-up for withdrawn subjects will not be done, unless the patient reaches out to us and would like to continue the therapy or study. At this point they would sign another consent form to agree to their continued participation.

F Study Procedures

F1 Screening for Eligibility

Consent process: If an interested participant contacts the research team about the study, a member of the research team will provide information about the study and required elements of consent over the telephone (see attached "Consent for Phone Screen") prior to obtaining the participants verbal consent. This phone screen will allow possible participants to ask questions and clarifications prior to coming in person for the in-person consent process. If a participant meets eligibility criteria for enrollment in the study based on their Initial Phone/Exclusion Screen and the participant indicates they wish to continue with the study, The participant will receive an email to complete the Word Pairs Checklist. The participant must consent to complete this questionnaire. If the participant is eligible following completion of the phone screen and questionnaire, the research team will notify the participant of their eligibility and ask whether they want to continue with the study. If the participant is unsure, the research assistant will provide unlimited time for the participant to consider whether they would like to participate in the study and a research assistant will notify the participant they can contact the research team if they would like to potentially participate in the future (they may have to re-complete the phone screen at that future time). If the person is still interested, the research team will schedule an in-person session.

F2 Visit 1

After the consent process, participants will be assessed for eligibility. After participants will have blood drawn and then have an EKG done. Then participants will be taken to the ERP (event related potential) room. Participants will wear an EEG cap and will complete three computer tasks during which EEG recordings will be obtained. The EEG cap takes 20 minutes to configure. Small dots of non-toxic gel are put on the head to connect the electrodes to the scalp. The participant will complete a Flanker Task, where participants start by seeing a fixation cross, and then a screen depicting a sets of arrowheads ("<<<<<", "<<><<", ">>>>>", or ">><>>"). Participants are instructed to press a key on the left or right side of the keyboard to indicate the direction of the center arrow. This allows for two congruent conditions ("<<<<<", ">>>>>") and two incongruent conditions ("<<><<", ">><>>"). Participants complete blocks of trials with breaks in between and told to respond as quickly and accurately as possible.This task takes approximately 15 minutes and behavioral responses will be recorded and EEG will be recorded during the task and used to measure the ERN. Participants will then complete the Doors Task, where they have chances to win or lose points (in reality, all participants will make the full amount of $5. Each trial will start with a screen with a fixation cross, followed by a screen with graphic of two doors side by side. Participants will be instructed that if they chose the correct door, they can accrue points, while if they chose the incorrect door, they lose points. Participants are told points will be tallied to make extra money they could make (in reality, all participants will make the full amount of $5). Participants will use a videogame controller and will see a screen with two doors and asked to

choose a door and the doors will remain on the screen until the participant chooses a door. Then a fixation mark is presented, followed by a feedback arrow: a green upward facing arrow indicates a correct guess (i.e., they won points), while a red downward facing arrow indicates an incorrect guess (i.e., they lost points). A fixation mark is then presented and then a screen that states, “Click for next round" is presented until a response in made. Behavioral responses will be recorded and EEG will be recorded during the task and used to measure the RewP. Participants will the complete 6 minutes of resting state EEG where they will keep their eyes closed for 1 minute, followed by eyes open for 1 minute, for 6 consecutive minutes where they will be told to ‘do nothing.’In total, the ERP portion of the task will take approximately 1.5 hours.

Following the ERP/EEG session, participants will meet with a researcher and complete a structured clinical interview, the Montgomery and Asberg Depression Rating Scale (MADRS) to assess current depressive symtpoms. Participants will also complete the Mini International Neuropsychiatric Interview (MINI) as part of this clinical interview as well. This should take approximately 30 minutes.

Participants will then sit at a computer and complete online questionnaires on REDCap. Questionnaires will take approximately 20 minutes and can be completed at home as well. Questionnaires include:

Acceptance and Action Questionnaire-II (AAQ-II): This measure assesses psychological inflexibility. Pathological Obsessive Compulsive Personality Scale (POPS): This measures personality traits related to the HPM/OC personality, including emotional overcontrol, perfectionism, rigidity. Social Connectedness Scale- Revised (SCS-R): This measure assesses the degree to which participants feel socially connected to others. UCLA Loneliness Scale Revised: This measures one’s subjective feelings of emotional and social loneliness. Temporal Experience of Pleasure Scale (TEPS): This measure assesses anticipatory pleasure and consummatory or outcome pleasure. Patient Health Questionnaire – 9 (PHQ-9): This is a measure of depressive symptoms. Generalized Anxiety Disorder Questionnaire – 7 (GAD-7): This is a measure of anxiety symptoms. Quality of Life Questionnaire (QOL) – A 16-item measure for assessing quality of life in groups with chronic illness. Personaly Need for Structure – This measures assesses the extent to which participants need structure in their daily lives. Social Safeness and Pleasure Scale – This measure assesses feelings of positive emotions and pleasure in social situations. Emotion Regulation Questionnaire (ERQ) – The Emotion Regulation Questionnaire (ERQ) was developed to measure two specific constructs related to emotion control: cognitive reappraisal and expressive suppression. The ERQ is a 10-item self-report measure employed to measure dispositional use of the emotion regulation strategies of emotional suppression and reappraisal. The items use a 7-point Likert scale with responses ranging from one (strongly disagree) to seven (strongly agree). Responses to Positive Affect (RPA) –. (RPA; Feldman et al., 2008). The RPA is a 17-item measure rated on a 1 (almost never respond in this

way) to 4 (almost always respond in this way) scale that assesses emotion regulation specifically during positive emotional experiences. The RPA has three factor-derived subscales, including Emotion-focused and Self-focused positive rumination and Dampening, which assesses ways positive emotion might be diminished (e.g., “Think about things that could go wrong”). The two positive rumination subscales are often studied in the context of bipolar disorder and are associated with elevated manic symptoms, while elevated dampening has been associated with both current and predictive depressive symptoms in both mood disordered (bipolar and depressed) and non-clinical populations (Johnson, McKenzie & McMurrich, 2008). In the current study we are using the Dampening eight item subscale only. Ask Suicide-Screening Questions (ASQ)- The ASQ is is a brief (5 questions) assessment to gauge suicide risk in participants. OC Trait Rating Scale – This scale assesses maladaptive aspects of the HPM/OC 'overcontrolled phenotype' that we will use to assess whether ketamine and RO DBT are targeting the mechanistic processes inherent in the overcontrolled phenotype.

Ketamine session questionnaires:
In addition to completing the above mentioned PHQ-9 and GAD-7 at each ketamine infusion, participants will also complete:

Brief Psychiatric Rating Scale- positive (psychotic) symptoms subscale (BPRS+): This measures transient neuropsychiatric changes that might occur in response to the ketamine infusions. KetRO Clinical Events Checklist: This measure assesses common adverse side effects of using ketamine. Clinical Administered Dissociative State Scale (CADSS) – Modified – This measure assesses dissociative symptoms after using ketamine.

Before the ketamine administration, participants will have vital signs collected in addition to and ECG and blood chemistry tests.

During the ketamine + RO DBT portion of the study, participants will also complete the PHQ-9 and GAD-7 following each RO DBT session. Following completion of the ketamine portion, and ongoing weekly RO DBT therapy, participants will complete the PHQ-9 and GAD-7 weekly following their individual therapy sessions.

At the end of treatment, participants will be asked to complete a post-treatment questionnaire. The participants’ therapists will also be asked to complete a separate end of therapy questionnaire.

Visit 2 etc.
The mid-treatment (post-ketamine) and post-RO DBT treatment in-person assessments will include the idendical ERP and questionnaire data.

Ketamine protocol:

Participants will be admitted to the Washington University Clinical Trial Research Unit (CTRU) to receive 0.5mg/kg intravenous ketamine given over 40 minutes, as is routinely done in ketamine treatment.(16) Participants will have same-room observation during and 1hr post-infusion to monitor blood pressure, oxygen saturation and to manage psychotomimetic adverse events by highly trained medical support staff. Side effects will also be monitored (e.g., light-headed, "high," exhilarated, perceptual changes, hallucinations, nauseated). If a participant is unable to receive IV ketamine (e.g., because of lack of IV access), he or she can receive IM ketamine as a bolus. The dosage will be the same (0.5 mg/kg) because its bioavailability is 93% and its plasma half-life is similar to IV. We will also use clonidine as needed, taken orally the night prior to or morning of infusion to prevent distressing symptoms. Ketamine is completely cleared from the body 15 hours later; thus, key personnel have deemed that infusions will take place 1-2 days prior to RODBT individual/group sessions to maximally enhance the plasticity and potentially catalyzing effects of ketamine on psychotherapy sessions.

Therapy:
RO DBT therapy includes attending weekly one hour therapy and weekly 1.5 hours skills class sessions for approximately 16 weeks. These weekly individual therapy sessions (but not skills class sessions) will be videotaped uploaded to the WUSTL Box.com website, which is secure and encrypted. Up to 15 participants can participate in this option. RO DBT helps individuals with HPM/OC relax rigid and extreme inhibitory control, be receptive and open to new experiences and feedback and increasing social connectedness by activating the social safety system. RO-DBT treatment themes include: 1) hyper-detail-focused and overly cautios behavior, 2), rigid and rule governed behavior 3) inhibited and disingenuous emotional expression 4) distant and aloof social connectedness and relationships and 5) high social comparisons and envy.

Clinicians will be Molly Fennig, BA, Cherie Massmann, MA, LPC, Michael Mullins, MSW, LCSW, Gregory Peebles, MA, LPC and Mariah Saldena, MA. Cherie Massman, Michael Mullins, Gregory Peebles and Mariah Saldena are all licenced therapists in the St. Louis community and Molly Fennig is a PhD clinical pychology graduate student in the Department of Psychology at Washington University. All clinicians have been intensively trained in RO DBT. Group skills classes will be run by both the PI, Kirsten Gilbert, Whig Mullins and/or another clinician. Paper notes will be kept in a locked file cabinet in locked offices. De-idnetified therapy notes will be uploaded to a secure Wustl box.com folder for the study. At the end of therapy, the clinician will complete an "End of Therapy Progress" questionnaire to assess progress made or not made across the research study. In addition, the participant will be contacted via phone call and asked several questions about their experience with RO DBT along with their perceptions of treatment outcomes. In addition, research team member will contact subjects who have dropped out of the study or who have completed treatment. The participant will be contacted via phone call to and invited to participate in a follow up interview. They will be asked several questions about their experience with

Ketamine enhanced RO DBT along with their perceptions of treatment outcomes. This will be conducted over zoom and be recorded or over the phone and audio recorded to an handheld recorder. The recording will be immediately transferred to wustl box, in a secured password protected account. The data from the recording wil be deleted immediately from the handheld recorder. At the end of the study a research team member will transcribe the recordings and save the transcriptions to a wustl box folder. All audio and video recordings will be deleted at that time.

G Statistical Plan

G1 Sample Size Determination and Power

Using G*Power, power for Aim 1 (MDD symptoms) was based on a) a pilot of RODBT from the PI, b) Lynch et al. (2020),[9] a multi-cite RCT of RODBT in TRD and c) Zarate et al (2006)[37], an original RCT of ketamine in TRD. With α=.05 and power of 80%, we would need a sample of 8 to detect an effect from RODBT, and n=5 with ketamine. For Aim 2, we used a) Baudinet et al (2021)[11] who tested RODBT change in behavioral flexibility and reward processing and b) a pilot of RODBT from the PI. With α=.05 and power of 80%, we would need a sample of 5-15 participants to detect behavioral change in mechanistic process. Power for neural change in HPM/OC has not been computed because no previous studies have targeted HPM/OC with ketamine. However, our sample is similar to other medication-assisted psychotherapy pilot studies.

G2 Interim Monitoring and Early Stopping

This is part of Analysis 1a below. Specifically, side effects and symptoms will be monitored at each ketamine and RO DBT session for 4 weeks while they are running concurrently. If there are any issues with running a ketamine session and a psychotherapy session within 1-2 days of each other, protocols can be modified or stopped, if necessary.

G3 Analysis Plan

Analysis 1a: No analyses will be completed for H1a; qualitative data from session questionnaires regarding side-effects, symptoms and functioning will be continually monitored, to assess if there is a need to modify protocols. **H1b:** Using individual session data, ketamine will catalyze psychiatric symptom change in RODBT and ketamine-enhanced RODBT will be associated with decreasing trajectories of depressive symptoms. Analysis 1b: Multilevel linear modeling (MLM) with random intercepts and slopes will model trajectories of depressive symptoms across treatment.

Aim 2: Examine preliminary efficacy of ketamine-enhanced RODBT in engaging neural and behavioral mechanistic targets in young adults with

moderate to severe depression.
H2a: Ketamine-enhanced RODBT will be associated with neural ERN reductions and neural RewP increases. Analysis 2a: Using baseline, mid- and post-treatment assessments, change in the ERN (and in a separate model, the RewP) will be assessed using a MLM. **H2b:** Ketamine-enhanced RODBT will be associated with behavioral cognitive flexibility, openness, reward responding and social functioning improvements. Analysis 2b: Using baseline, mid- and post-treatment assessments, change in behavioral mechanisms will, similar to Analysis 2a, be assessed using a MLM.

G4 Statistical Methods

See above

G5 Missing Outcome Data

If missing outcome data exists, that participant will be excluded for that analysis. Of note, when modeling data, missing data does not mean the participant can be excluded.

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