Perturbation of the Depression Connectome (PDC) 1.0 Data Release: Reference Manual

27 April 2023

A Connectomes Related to Human Disease Project:
Perturbation of the treatment resistant depression connectome by fast-acting therapies

Project Number:
U01MH110008-04

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1. INTRODUCTION

This collection of data was acquired according to the goals of a Connectomes Related to Human Disease (CRHD) U01 Project titled "*Perturbation of the treatment resistant depression connectome by fast-acting therapies, MH110008*." The data being shared through the NDA include multimodal MRI data collected using image acquisition protocols identical to the Human Connectome Lifespan Project for Aging (HCP-A, U01AG052564), with the exception of one of the two fMRI tasks administered. Demographic and behavioral measures collected for this CRHD cohort also overlap with the HCP-A project, though the diagnostic and clinical assessments collected are unique to this project, which includes patients with major depressive disorder (MDD). However, some of these MDD-specific assessments are similar to those used for other independent CRHD projects that are also focused on mood and anxiety disorders[1].

2. BACKGROUND

2.2 Objective

The primary goal of this Connectomes Related to Human Disease (CRHD) U01 titled "*Perturbation of the treatment resistant depression connectome by fast-acting therapies,* MH110008," or Perturbation of the Depression Connectome (PDC) study is to leverage the optimized MRI technologies of the NIH-funded Human Connectome Project (HCP) to address how interventions with rapid and robust effects on mood and behavior modulate brain networks (or the connectome) in major depression.

The specific objectives of this CRHD project are to 1) identify connectome-specific correlates and predictors of treatment outcome to electroconvulsive therapy (ECT), serial ketamine treatment and experimental total sleep deprivation (TSD), which each have rapidly-acting antidepressant effects via neurostimulation, pharmacological or behavioral perturbation, and to 2) characterize alterations in neural connectivity associated with individual clinical, behavioral or physiological factors that distinguish patients with severe depression from non-depressed controls.

2.3 Significance

Depression is *the number one* cause of disability worldwide. Of patients seeking treatment, up to a third will remain unresponsive to multiple protracted trials of conventional therapies[2]. Such patients, referred to as having treatment resistant depression (TRD)[3,4], are more likely to be hospitalized, have more outpatient visits, greater psychotropic medication usage and are at increased risk for suicide[3]. Investigating how interventions capable of eliciting fast-acting antidepressant effects modulate the human connectome in individual depressed patients could elucidate mechanisms underlying rapid clinical response that may inform clinical practice for other depressed patients. Further, in line with the overarching goals of the NIMH Research Domain Criteria (RDoC) Initiative, through extensive characterization of imaging and behavioral phenotypes paired with analyses of gene function, it may be possible to determine if imaging, physiological and behavioral profiles unique to particular patients may better guide personalized treatment.

For this CRHD project, MRI acquisition protocols including structural, resting-state/task functional, diffusion and perfusion MRI sequences were harmonized with the HCP-Aging Lifespan project (HCP-A, U01AG052564)[5,6]. Behavioral testing batteries were also modeled to overlap with the HCP Lifespan projects with additional scales added for diagnostic screening, as well as measures of clinical state over time in individuals with major depression receiving treatment[1]. This project included three separate cohorts of patients with major depression assessed before and after receiving one of three rapidly-acting interventions, including

ECT, ketamine infusion or TSD[1]. The study design is naturalistic such that patients were assigned to each intervention based on clinical decisions rather than randomized to receive different treatments. Since average response to each intervention is known to vary across time, follow-up assessments were performed at different time points depending on the intervention.

This CRHD project has two arms, one longitudinal and one cross-sectional. For the longitudinal arm, patients received imaging and clinical/behavioral assessments before and after completing an ECT index series, four serial ketamine infusions or one night of TSD. With intramural support from the UCLA Depression Grand Challenge (DGC) initiative (https://grandchallenges.ucla.edu/depression/), additional time points were added for ECT patients at 3-months post treatment or relapse (whichever was sooner), and for ketamine patients after single ketamine infusion, and at 5-weeks post treatment or relapse (when possible). A subsample of controls was assessed twice without intervention to allow estimation of the variance associated with repeat scanning, and a subsample of controls were assessed after receiving TSD. Data from a sample of non-depressed controls were obtained to address cross-sectional hypotheses involving comparisons between patients with depression and control subjects. Control data drawn from the HCP-A project collected with the same MRI protocols is intended to augment the project-specific non-depressed control group collected for this CRHD to provide greater power for future cross-sectional analyses [Fig 1].

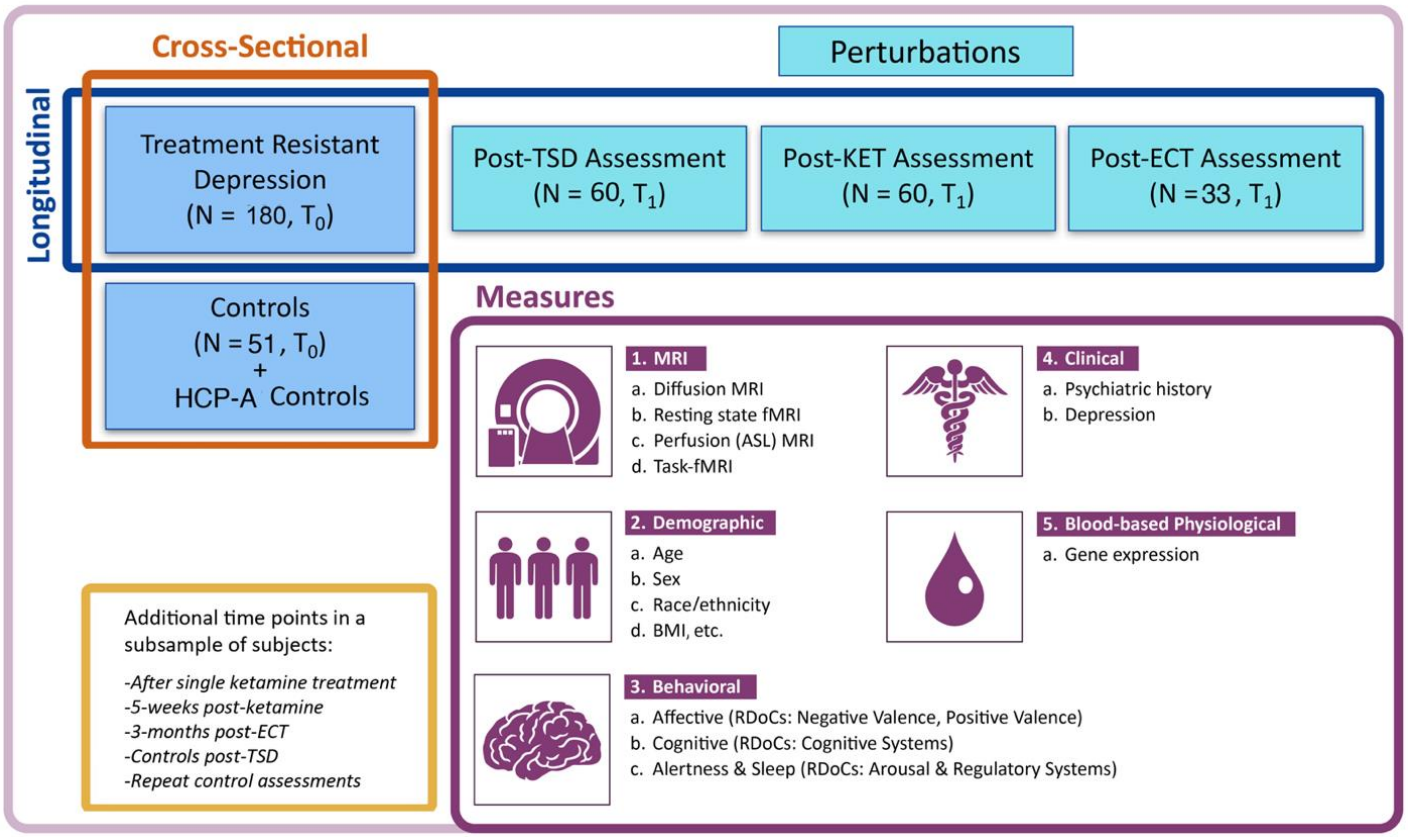


Figure 1. Illustration of the cross-sectional and longitudinal components of this project. N=180 patients and N=51 controls were assessed at baseline. N=60 patients were assessed after receiving TSD, N=60 patients were assessed after receiving serial ketamine infusions, and N=33 patients were assessed after receiving an index series of ECT. Additional time points were obtained for a subsample of participants as listed. All subjects received multimodal MRI scanning and behavioral and clinical assessments at each time point.

ECT (brain stimulation), ketamine infusion (pharmacological), and TSD (behavioral) each elicit rapid and pronounced antidepressant effects and have distinct access to the central nervous system (CNS) to acutely perturb brain architecture. These interventions are thus ideal for determining both unique and overlapping mechanisms and predictors of antidepressant response occurring in neural circuitry downstream of molecular/cellular effects.

3. RESEARCH SITE

All data were collected at a single site on the same 3T Prisma system at the University of California, Los Angeles (UCLA). A total of 231 participants completed study procedures and are included in the April 2023 PDC Release on NDA. Note: HCP-A and HCP-D both include participants scanned at UCLA using identical MRI protocols. Data from these participants (148 HCP-A, 128 HCP-D subjects) are available as part of the NDA LS 2.0 Release (2/26/21).

MRI scans took place at the UCLA Ahmanson-Lovelace Brain Mapping Center (ALBMC).

Serial ketamine infusions took place at either the UCLA Clinical and Translational Research Center (CTRC) or the Ronald Reagan Medical Center's ECT Clinic.

ECT was administered at the UCLA Ronald Reagan Medical Center's ECT Clinic.

Overnight sleep deprivation visits for TSD took place at the UCLA Clinical and Translational Research Center (CTRC).

3.2 Participants

Participants comprised of 3 separate treatment cohorts of patients with depression, and controls:

- N=180 patients completed baseline assessments irrespective of intervention
- N=60 patients completed serial ketamine infusion
- N=60 patients completed TSD
- N=33 patients completed ECT

- N=51 non-depressed healthy controls completed baseline measures
- N=16 controls completed TSD
- N=17 controls completed repeat assessments with no intervention

3.3 Recruitment

All research subjects were recruited from the Los Angeles area through advertisements, clinician referral, or clinicaltrials.gov (NCT02165449), for ketamine treatment specifically. Participants in the ECT study were recruited from amongst those individuals who were already scheduled to receive ECT as part of their routine care at the Resnick Neuropsychiatric Hospital at UCLA (R-NPH). ECT participants were both inpatients and outpatients. Eligibility for ECT was independently verified based on clinical indications according to the APA ECT Task Force Report guidelines. ECT treatment was not manipulated for this study and was provided as clinically indicated.

3.4 Inclusion and Exclusion Criteria

Male and female subjects meeting DSM-5 criteria for major depressive disorder and healthy control subjects were enrolled. Inclusion and exclusion criteria for each of the three interventions (serial ketamine treatment, ECT or TSD) and for controls are listed below.

3.4.1 Serial Ketamine Infusion Therapy

Inclusion Criteria:

- 20-64 years old
- Able to give informed consent
- DSM-5 criteria for non-psychotic major depression met
- Treatment resistant (failure to achieve therapeutic response to at least two trials of antidepressant medication of sufficient dose used for at least 4-6 weeks each, as determined by the Antidepressant Treatment History Form)
- Recurrent depression, with current depressive episode lasting for at least 6 months
- Stable medications for past 6 weeks
- Under care of psychiatrist, acknowledges study participation
- Be amenable (as judged by treating psychiatrist) to tapering benzodiazepines (only) starting the night before either a scan session or ketamine infusion

Exclusion Criteria:

- Psychotic reactions to medications, alcohol or illicit substances in the past
- If bipolar, rapid cycling (as defined by four or more episodes of mania or depression in one year)
- Mental retardation or other developmental disorder
- Comorbid substance abuse or dependence in past 3 months
- Serious or unstable medical or neurological condition(s) that in the opinion of the PI renders ketamine unsafe to administer
- Contraindications to MRI scanning
- If female, pregnant (as confirmed by positive urine pregnancy test) or planning on becoming pregnant
- Diagnosis of dementia of any type
- Actively suicidal as determined by HAMD-17 item 3 score of 4, within past month requiring psychiatric hospitalization, or clinical judgment
- Schizophrenia or schizoaffective Axis 1 diagnosis, Psychotic disorder due to general medical condition
- History of convulsions or withdrawal seizures
- Any neuromodulation treatment, ketamine or total sleep deprivation within past 6 months

3.4.2 Electroconvulsive Therapy

Inclusion Criteria:

- 20-75 years old
- Can read and understand English
- Able to give informed consent
- DSM-5 criteria for major depression met
- Already scheduled to receive ECT as part of their routine care at the Resnick Neuropsychiatric Hospital at UCLA.

Exclusion Criteria:

- If bipolar, rapid cycling (as defined by four or more episodes of mania or depression in one year)
- Mental retardation or other developmental disorder
- Comorbid substance abuse or dependence in past 3 months
- Contraindications to MRI scanning (metal implants, pregnancy, claustrophobia)
- Diagnosis of dementia of any type

- Schizophrenia or schizoaffective Axis 1 diagnosis, Psychotic disorder due to general medical condition
- History of convulsions or withdrawal seizures
- Any neuromodulation treatment, ketamine or TSD within past 1 month
- 1 month since previous participation in an ECT or ketamine research study at UCLA

3.4.3 Total Sleep Deprivation (Depressed Participants)

Inclusion Criteria:

- 20-64 years old
- Can read and understand English
- Able to give informed consent
- DSM-5 criteria for major depression met
- Recurrent depression, with current depressive episode lasting for at least 6 months
- Stable medications for past 6 weeks
- Be amenable (as judged by treating psychiatrist) to tapering benzodiazepines (only) at least 72 hours prior total sleep deprivation

Exclusion Criteria:

- History of manic switching while on mood stabilizers
- If bipolar, rapid cycling (as defined by four or more episodes of mania or depression in one year)
- Mental retardation or other developmental disorder
- Comorbid substance abuse or dependence in past 3 months
- Serious or unstable medical or neurological condition(s) that in the opinion of the PI renders sleep deprivation unsafe to administer
- Contraindications to MRI scanning
- If female, pregnant (as confirmed by positive urine pregnancy test) or planning on becoming pregnant
- Diagnosis of dementia of any type
- Actively suicidal as determined by HAMD-17 item 3 score of 4, within past month requiring psychiatric hospitalization, or clinical judgment
- Schizophrenia or schizoaffective Axis 1 diagnosis, Psychotic disorder due to general medical condition
- History of convulsions or withdrawal seizures
- Any neuromodulation treatment, ketamine or total sleep deprivation within past 6 months

3.4.4 Healthy Controls

Healthy controls were assessed at baseline, a subsample received follow-up assessments without intervention or after receiving TSD.

Inclusion Criteria:

- 20-64 years old
- Can read and understand English
- Able to give informed consent
- No history of depressive disorder or bipolar disorder that is current, recurrent, or with a single episode that lasted longer than one year

- Have not used antidepressants or mood stabilizers within the past 6 months

Exclusion Criteria:

- Current or recurrent, or prior diagnosis of major depressive disorder or bipolar disorder within the last 10 years
- Past use (within the last 6 months) of antidepressants/mood stabilizers or illicit substances
- Substance abuse
- Schizophrenia or schizoaffective Axis I diagnosis
- Psychotic disorder due to general medical condition
- Unable to read and understand English
- Pregnancy
- Contraindication to scanning
- Mental retardation
- Dementia
- Neurological condition associated with brain abnormalities (e.g., traumatic brain injury, recent stroke, tumor)
- Serious uncontrolled medical illness
- Related to another study participant based on self-report
- Does not agree to have their de-identified data shared

4. STUDY PROCEDURES

Patients were assigned to treatment with ketamine, ECT or TSD based on clinical determinations using a naturalistic study design rather than randomizing patients to a particular treatment condition. Patients receiving ECT were scheduled to receive ECT independent of this research study. Study research procedures included clinical interviews or questionnaires administered by trained study personnel or completed independently by the subject, and multimodal MRI scanning.

4.2 Treatment Protocols

All enrolled participants received baseline/pre-treatment research assessments. Since peak response to each rapidly-acting treatment intervention included in the protocol varies across time (e.g., hours versus weeks), longitudinal follow-up assessments were performed at different time points depending on whether patients received ECT, ketamine infusion, or TSD.

4.2.1 ECT

For ECT, follow-up MRIs and clinical/behavioral assessments were conducted within one week of patients completing the ECT index series that occurred approximately 3-4 weeks following treatment initiation. A subsample of ECT patients received a final study visit when possible either three months after ECT index treatment ended or upon symptom recurrence, whichever occurred first. ECT (5000Q MECTA Corp) was administered using standard clinical protocols, which were not manipulated for this study. The seizure threshold was individually titrated at the first ECT session. All patients received right-unilateral ECT (pulse width: 0.3 ms, amplitude: 800 mA). If clinically determined, subjects were subsequently switched to bitemporal ECT (pulse width: 0.5 ms, amplitude: 8,000 mA). ECT, administered 2–3 days apart, continued until patients achieved maximal response or remission for at least a week as evaluated by mood scales and assessment by an expert ECT Psychiatrist.

The data timepoints are defined as such:
01 = Baseline

02 = Post-treatment assessment (after ECT index series completed)
03 = Follow-up

4.2.2 Ketamine

For ketamine, a subanesthetic dose (0.5 mg/kg) of ketamine diluted in 60cc saline was delivered intravenously via pump over 40 min. Vital sign monitoring during infusion included blood pressure, pulse oximetry, and respiratory rate recording every 3 min and a continuous cardiac rhythm strip. Mental status monitoring assessed for any untoward behavioral or psychological effects. Post-treatment MRIs and clinical/behavioral assessments occurred 24 h after patients completed four serial ketamine infusions that were administered 2-3 times weekly, similar to the ECT schedule. Supplemental MRI and clinical/behavioral follow-up assessments were also obtained for a majority of ketamine subjects 24 h after they had received their first ketamine infusion, and five weeks after their fourth infusion or upon symptom recurrence, whichever occurred first.

The data timepoints are defined as such:
01 = Baseline
02 = 24h Post-first infusion
03 = 24h Post-last infusion
04 = Follow-up

4.2.3 TSD

For TSD, follow-up MRI scans and clinical/behavioral assessments took place directly after the overnight sleep deprivation session, occurring 23–25 h after baseline and at least 36 h of wakefulness. TSD patients completed clinical assessments 1-week after sleep deprivation though MRIs were not collected at this time point.

The data timepoints are defined as such:
01 = Pre-TSD (immediately before the overnight session)
02 = Post-TSD (immediately after the overnight session)

4.2.4 Controls

The majority of non-depressed controls were assessed at baseline only, though a subsample received repeat assessments:

- A subsample of controls were also assessed after receiving TSD using the protocol for patients described above.
- A separate subsample of controls received repeat scans approximately two weeks after baseline without any intervention.

The data timepoints are defined as such:

01 = Baseline
02 = Follow-up

The timing of research assessments relative to the three fast-acting antidepressant interventions are illustrated in Fig 2 (modified from [1]).

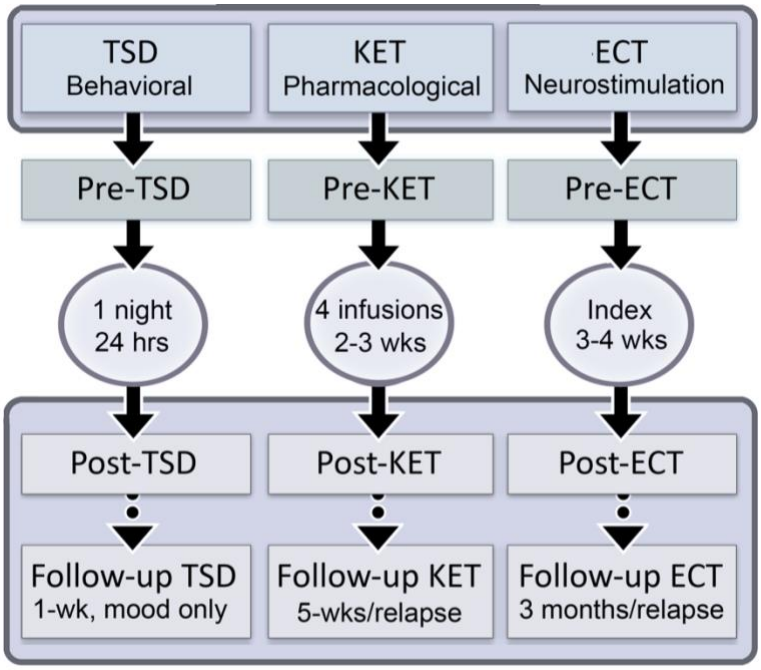


Figure 2. Timing of pre- and post-treatment MRI and clinical/behavioral assessments for each intervention including total sleep deprivation (TSD; a behavioral intervention), serial ketamine infusion (KET; a pharmacological intervention) or electroconvulsive therapy (ECT: neuromodulation)

4.3 Clinical and Behavioral Assessments

Clinical assessments and questionnaires were administered to all subjects regardless of whether they received a particular intervention unless otherwise specified. Research visits including clinical assessments, questionnaires, NIH Toolbox measures, and other cognitive assessments took place at the UCLA Semel Institute for Neuroscience and Human Behavior.

4.3.1 Consult and Research Assessment Visits

Initial eligibility screening performed by phone was followed by a Consult visit, and subsequent Research Assessment study visits at baseline and follow-up study time points.

4.3.1.1 Consult Visits

A telephone screening interview conducted prior to the Consult visit was used to determine basic eligibility for the study. The Consult visit was used to determine final eligibility. The Consult visit included clinical and diagnostic interviews administered by trained study staff, labs (blood draw, EKG, urine), and a consultation with the study physician (described further below).

Participants were screened to ensure that study eligibility criteria were met, and that there were no contraindications to treatment (prescription of ECT treatment was determined independently of this study) or MRI scanning.

Consult visits took approximately five hours to complete. Clinical assessments (e.g., diagnostic interview, mood scales) took up to four hours, and all other consult visit activities (e.g., lab visit) took approximately one hour.

4.3.1.2 Research Assessment Study Visits

On average, research assessment study visits took up to six hours to complete. Clinical assessments (e.g., HDRS) took one hour, MRI scans took up to two hours, NIH Toolbox (NIHT) measures took up to one hour, and all other study visit activities and measures (e.g., questionnaires, lab visits) took up to two hours. All subjects were given breaks as needed. All measures were collected on the same day as the MRI scan for baseline or follow-up time points.

With a few exceptions, baseline/pre-treatment visits were scheduled within one week of Consult for the Ketamine and TSD, and within two weeks of Consult for the first ECT treatment.

4.3.2 Diagnostic Interviews

The Structured Clinical Interview for DSM-5-Resesarch Version (SCID-5-RV)[7] was administered to both patients and healthy controls by trained raters at the Consult Visit.

In patients, the SCID-5-RV[7] was used to rule out participants who did not meet DSM-5 criteria for non-psychotic major depression and recurrent depression, or who met criteria for rapid cycling in Bipolar disorder, comorbid substance abuse or dependence in past three months, schizophrenia or schizoaffective Axis 1 diagnosis, psychotic disorder due to general medical condition, or were actively suicidal in the past month.

In healthy controls, the SCID-5-RV[7] was used to confirm that participants had no history of depressive disorder or bipolar disorder that is current, recurrent, or with a single episode that lasted longer than one year. In addition, it was used to screen for current, recurrent, or prior diagnosis of major depressive disorder or bipolar disorder within the last 10 years, past use (within the last 6 months) of illicit substances, substance abuse, schizophrenia or schizoaffective Axis I diagnosis, and psychotic disorder due to general medical condition.

Participants' diagnostic and medication histories were recorded during the consult visits. Diagnostic history assessed lifetime and current psychiatric clinical symptoms (including substance use) and included age of first depressive episode, number of previous episodes, and duration of current episode. Medication history assessed current and past medication use. Out of a list of possible medications, subjects reported whether they had taken a medication in the past 3 months, 12 months, or in their lifetime; and if so, dates/duration recorded.

4.3.3 Laboratory Tests

Participants received measurement of vital signs (e.g., BP, HR, temperature), a blood draw to determine metabolic, kidney and liver function, EKG, and provided a urine sample for drug and pregnancy (women) screening. The study physician reviewed lab results to ensure there were no contraindications to participating.

4.3.4 Cognitive Measures

4.3.4.1 NIH Toolbox Measures

The following battery was included from the NIH Toolbox[8,9]:

Cognition

- Picture Sequence Memory Test **(psm01)**
- Dimensional Change Card Sort Test **(dccs01)**
- Flanker Inhibitory Control and Attention Test **(flanker01)**
- Picture Vocabulary Test **(tpvt01)**

- Pattern Comparison Processing Speed Test **(pcps01)**
- List Scoring Working Memory Test **(lswmt01)**
- Oral Reading Recognition Test **(orrt01)**

Emotion (not uploaded to NDA)

- Psychological Well-Being
- Social Relationships/Satisfaction
- Stress and Self-Efficacy
- Negative Affect
- Pain
- Pain Intensity Survey
- Pain Interference Survey

4.3.4.2 Other HCP Lifespan Measures

- Penn Emotion Recognition Task (ERT)[10]. **(er4001)**
- Matrix Reasoning Task (MRT) *(not uploaded to NDA)*

4.3.4.3 Autobiographical Memory Test (AMT) *(not uploaded to NDA)*

The AMT[11] is a cuing paradigm used to elicit autobiographical memories. Typically, participants are presented with cue words (generally words of positive and negative valence) and are asked to come up with unique specific memories from their personal past in response to the cues within 30 seconds. This data is not uploaded to or shared through the NDA.

4.3.5 Clinical Scales

4.3.5.1 Hamilton Depression Rating Scale (HAM-D, or HDRS)[12].

The Hamilton Depression Rating Scale[12] is the most widely used clinician-administered rating scale for primary depressive illness. The original version contains 17 items (HDRS17) assessing symptoms of depression experienced over the past week. The HDRS was originally developed for hospital inpatients, hence the emphasis on melancholic and physical symptoms of depression. The HDRS17 does not assess for atypical symptoms of depression (e.g., hypersomnia, hyperphagia).

In the HDRS17, nine items (depressed mood, guilt, suicide, work and activities, retardation, agitation, anxiety (psychic), anxiety (somatic), and hypochondriasis) are scored on a scale of 0-4. Eight items (early, middle, and late insomnia, somatic symptoms (gastrointestinal), somatic symptoms (general), genital symptoms, loss of weight within the last week, and insight) are scored on a scale of 0-2. Individual item scores are added to obtain a total score. Item-level responses and scores for this measure can be found in the NDA data structure **hrsd01**.

Scoring notes: In cases where participants did not meet the cutoff score for eligibility after administration of the HDRS17 at the Consult visit, additional items from the HAM-D 28 pertaining to symptoms of atypical depression were assessed. HAM-D 28 includes 7 additional questions: fatiguability, social withdrawal, appetite increase, increased eating, carbohydrate craving or eating, weight gain, and hypersomnia. Participants were excluded if they scored below 17 at Consult in the Ketamine study, and below 14 at Consult in the TSD study.

Given the repeated assessments made in our studies over a short period of time, two versions of HDRS were used but the scoring was kept consistent across time points. The following rule was applied across studies: if an

assessment was made within 24 hours of the previous assessment, the shortened version, which omits asking questions about Mood Variation, Mood Quality, Early Insomnia, Middle Insomnia, Late Insomnia, Hypersomnia, Sexual Interest, and Weight, was used. The total score was calculated using the short version responses at this time point plus the responses to the omitted items from the full version that were asked less than 24 hours ago (e.g., those scores from Pre-TSD assessment).

For TSD participants, the full version of the HDRS17 was used at Consult and at Pre-TSD. The time frame for symptom assessment was in the past week. At Post-TSD (which is ~24 hours since last assessment), the full version was used, but with revised scoring instructions on the insomnia items. The time frame for recording symptoms was since last assessment. The Pre-TSD time point is distinct from the Consult time point, so here reference was made to Consult scores for calculating Pre-TSD scores.

- Modified HDRS score: Omit 3 sleep-related items from total score calculation because they are rated differently for Post- treatment assessments.
- Estimated Total HDRS : Sleep-related items carried over for total score calculation.

For serial Ketamine participants, repeated assessments occurred >24 hours after the previous assessment, thus the full version of the HDRS17 was used for all assessments. At Consult and at Baseline, the time frame for symptom assessment was in the past week. At Post-treatment, the full version was used with revised scoring instructions on the insomnia items. The time frame for recording symptoms was since the last assessment.

- Modified scores: Omit 3 sleep-related items from total score calculation because they are rated differently for Post- assessments.

For ECT participants, the full version was used for all assessments and the time frame for symptom assessment was in the past week.

4.3.5.2 Quick Inventory of Depressive Symptomatology (QIDS)

The Quick Inventory of Depressive Symptoms[13] is a 16-item self-report measure that covers nine diagnostic symptom domains and is sensitive to symptom changes over narrow time intervals. Participants are instructed to choose the response to each item that best described them in the past seven days. Each item is scored on a scale from 0-3.

Scoring notes: Given the repeated assessments made in our studies over a short period of time, two versions of QIDS were used but the scoring was kept consistent across time points. The following rule was applied across studies: if an assessment was made within 24 hours of the last assessment, the shortened version was used, which omits asking questions about Increase/Decrease in Weight. The total score was calculated using responses from the short version at this time point plus the responses to the omitted items from the full version that were asked less than 24 hours ago.

For TSD participants, the full version of the QIDS was used pre-TSD. For the Post-TSD assessment, the shortened version was used. Items were omitted that assessed sleep and weight, which are not expected to change in a 24-hour period. Scores for the omitted items were used from the most recent full QIDS assessment (pre-TSD) for calculations.

For scoring, the total score is calculated by adding the following items: the highest score on any one of the 4 sleep items (1-4), 5, the highest score on any one of the appetite/weight items (6-9) (score for 6 OR 7, and score for 8 OR 9), 10-14, the highest score on either of the two psychomotor items (15 and 16).

Scores for both the full and shortened versions of the QIDS range from 0-27. Item-level responses and total scores for this measure can be found in the NDA data structure **qids01**.

4.3.5.3 Depression Anxiety Stress Scales (DASS)

The DASS-14[14,15] is the 14-item subscale of the DASS-21 that measures anxiety and stress symptoms. It is a self-report questionnaire where participants are instructed to choose a response that indicates how much a statement applied to them in the past week.

14 items are rated on the following scale:

- 0 = Did not apply to me at all
- 1 = Applied to me to some degree, or some of the time
- 2 = Applied to me to a considerable degree, or a good part of time
- 3 = Applied to me very much, or most of the time

Two subscale scores are calculated by adding the following items:

- Stress: 1, 4, 6, 8, 9, 10, 12.
- Anxiety: 2, 3, 5, 7, 11, 13, 14.

Scores for both the stress and anxiety subscales range from 0-21. Item-level responses and total stress and anxiety scores for this measure can be found in the NDA data structure **dass01**.

4.3.5.4 Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS[16,17] is a 14-item self-report measure assessing four domains of pleasure response/hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink. The SHAPS measures the degree to which a person is able to experience pleasure or the anticipation of a pleasurable experience. Participants are instructed to indicate how much they agree or disagree with each statement.

Items are scored on the following scale:

- Strongly Disagree = 1
- Disagree = 1
- Agree = 0
- Strongly Agree = 0

Scores range from 0-14. A total score is obtained by summing the 14 items, with a higher score indicating higher levels of anhedonia. Item-level responses and scores for this measure can be found in the NDA data structure **shaps01**.

4.3.5.5 Behavioral Inhibition System/Behavioral Activation System (BIS/BAS)

The BIS/BAS[18] is a 24-item self-report questionnaire measuring two motivational systems underlying behavior: the behavioral inhibition system (BIS; motivation to avoid aversive outcomes), and the behavioral activation system (BAS; motivation to approach desirable/goal-oriented outcomes). Participants are instructed to indicate how much they agree or disagree with each statement.

Items are scored on the following scale:

- 1 = Very true for me

- 2 = Somewhat true for me
- 3 = Somewhat false for me
- 4 = Very false for me

Items other than 2 and 22 are reverse-scored.

Four subscale scores are calculated by adding the following items:

- BAS Drive: 3, 9, 12, 21 (scores range from 4-16)
- BAS Fun Seeking: 5, 10, 15, 20 (scores range from 4-16)
- BAS Reward Responsiveness: 4, 7, 14, 18, 23 (scores range from 5-20)
- BIS: 2, 8, 13, 16, 19, 22, 24 (scores range from 7-28)
- Items 1, 6, 11, 17, are fillers.

Item-level responses and scores for this measure can be found in the NDA data structure **bisbas01**.

4.3.5.6 Munich ChronoType Questionnaire (MCTQ)

In our studies, a single item assessing Morningness vs. Eveningness (or chronotype) was used, based on evidence that this single item adequately captures ChronoType phenotype[19] without the need to collect remaining items that are redundant with PSQI.

Participants were asked to indicate if they considered themselves to be:

- Definitely a 'morning' person (coded as Morning person)
- More of a 'morning' than 'evening' person (coded as Morning person)
- More of an 'evening' than 'morning' person (coded as Evening person)
- Definitely an 'evening' person (coded as Evening person)
- Do not know

Because the single item chronotype did not map to an NDA data structure, we did not upload this data. The NDA data structure **mctq01** that is included in the behavioral data can be ignored as it does not contain any data values.

4.3.5.7 Pittsburgh Sleep Quality Index (PSQI)

The PSQI[20] is a 19-item self-report measure assessing sleep quality over a 1-month time period. Participants are instructed to indicate the most accurate reply for the majority of days and nights in the past month. Seven component scores are generated from the 19 items: subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. Items are scored on a 0-3 interval scale. A global PSQI score (range 0-21) is obtained by adding the seven component scores, with lower scores correlating to better sleep quality.

In our studies, research assessments were conducted more frequently than once per month. To avoid repeated administrations of the PSQI every few days, but still assess sleep quality pre- and post-treatment, the PSQI was administered at the following time points:

- TSD: Pre-TSD Baseline and Follow-up sessions
- Ketamine: Baseline, Post-Last Infusion, and Follow-up sessions
- ECT: Baseline, Post-Treatment (after ECT index treatment completed), and Follow-up sessions

For assessments that occurred within one month of the previous assessment, the question wording was changed to "since your last assessment".

Item-level responses for this measure can be found in the NDA data structure **psqi01**.

4.3.5.8 Fagerstrom Test for Nicotine Dependence

The Fagerstrom Test for Nicotine Dependence[21] is a six-item self-report measure assessing nicotine consumption, intake habits, and nicotine dependence in adults who are currently smokers or have been in the past two years. In our studies, if participants were not current smokers or had not been a current smoker in the past two years, they did not complete the measure and an automatic score of 0 was assigned. A total score was calculated by adding the scores for each individual item. Data for this measure can be found in the NDA data structure **fagerstrom01**.

4.3.5.9 World Health Organization Disability Assessment Schedule (WHODAS-12)

The WHODAS[22] is a 12-item self-report measure assessing difficulties due to health conditions over the past 30 days. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs. Participants are instructed to think back over the past 30 days and answer the questions thinking about how much difficulty they had doing the activities listed.

The 12 items are scored on the following scale:

- 1 = none
- 2 = mild
- 3 = moderate
- 4 = severe
- 5 = extreme

Scores range from 12-60. A total score is obtained by summing the scores for each item. A higher score indicates greater disability. Item-level responses and scores for this measure can be found in the NDA data structure **who01**.

4.3.5.10 Comorbidity Questionnaire (National Network of Depression Centers (NNDC))

The Comorbidity Questionnaire[23] is a 15-item self-report measure recording 15 conditions medically relevant to depression (e.g., thyroid disease). Participants are asked to indicate whether they have a condition, and if so, they are asked to indicate whether they are receiving treatment (such as medications) for the condition and whether the condition limits any of their activities. All items are scored using a Yes/No scale, and scores range from 0-15. Item-level responses for this measure can be found in the NDA data structure **sacq01**.

4.3.5.11 Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory[24] is an eight-item self-report measure assessing handedness. Participants are instructed to mark which option best describes the hand they use for the eight activities in question (writing, throwing, scissors, toothbrush, knife (no fork), spoon, striking a match, computer mouse).

The items are scored on the following scale:

- Always Left

- Usually Left
- No Preference
- Usually Right
- Always Right

To obtain a final score, the sums for total number of right-handed, left-handed, and no preference responses are calculated and inserted into the following formula: (Right - Left) / (Right + Left). The range is from -1 (Pure Left-hander) to +1 (Pure Right-hander). If a participant answers "No Preference" for all items, an automatic score of 0 is assigned. Item-level responses and scores for this questionnaire can be found in the NDA data structure **edinburgh_hand01**.

4.3.5.12 Apathy Evaluation Scale (AES)

The AES[25] is an 18-item self-report measure assessing apathy (lack of motivation) in adults. To detect apathy, 3 specific changes must be identified: (1) observable activity; (2) thought content; and (3) emotional responsivity. The AES includes items to evaluate diminished goal-directed overt behavior, cognitive evidence of apathy, and emotional evidence of apathy. Participants are instructed to select the option which best describes their thoughts, feelings, and activities for each statement in the past four weeks.

The items are scored on the following scale:

- 1 = Not at all
- 2 = Slightly
- 3 = Somewhat
- 4 = A lot

Higher scores indicate more apathy (thus, less motivation). Therefore, all items, except items 6 (“I put little effort into anything”), 10 (“Someone has to tell me what to do each day”), and 11 (“I am less concerned about my problems than I should be”), are reverse-scored such that the responses are scored as follows:

- 1 = A lot
- 2 = Somewhat
- 3 = Slightly
- 4 = Not at all

Scores range from 18-72. A total score is obtained by summing the scores for each item. Item-level responses and scores for this measure can be found in the NDA data structure **apath01**.

4.3.5.13 Measures of dissociative state and side effects specific to Ketamine treatment

Note: these measures were administered 45 minutes to 1 hr. after infusion treatment. The data for these measures has not been uploaded to or shared through the NDA.

Clinician Administered Dissociative States Scale (CADSS)

The CADSS[26] is a 28-item rater-administered scale assessing dissociative states at specific points in time. The instrument contains both subjective and objective items. This is intended to capture the fact that dissociation is both a subjective experience as well as a set of behaviors that can be observed by an outside observer. In the Ketamine study, only the 23 subjective items are used. A total score is obtained by summing the scores for each item.

The items are scored on the following scale:

- 0 = Not at all
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Generic Assessment of Side-Effects (GASE)

The GASE[27] is a 36-item self-report measure assessing recent side effects participants may have experienced in response to a certain treatment. In the Ketamine study, since the GASE is administered after each infusion treatment, the following 10 items did not apply and were excluded: hair loss, constipation, reduced appetite, increased appetite, difficulty urinating, problems with sexual performance or sex organs, painful or irregular menstruation, tendency to develop bruises, insomnia/sleeping problems, and nightmares or abnormal dreams. Additionally, the first question asking about symptom intensity was excluded. Participants are instructed to indicate whether they experienced any of the listed complaints due to the ketamine infusion they just received, and if so, to rate the severity of each complaint endorsed.

The complaints are first endorsed by using a Yes (present)/No (absent) scale. Endorsed items are then rated on the following scale:

- 1 = Mild
- 2 = Moderate
- 3 = Severe

A total score is obtained by summing the scores for each endorsed item.

Psychotomimetic States Inventory (PSI)

The PSI[28] is a 48-item self-report measure assessing psychotomimetic states in the moment following psychoactive drug use. In our study, the PSI was administered 45 minutes post-infusions. Participants are instructed to indicate the degree to which the statements best describe their experience at that moment.

Items are scored on the following scale:

- 0 = Not at all
- 1 = Slightly
- 2 = Moderately
- 3 = Strongly

Items 1, 6, 18, and 29 are reverse scored. Six sub-scale scores are calculated by adding the following items:

- Delusional Thinking (8 items): 4, 12, 19, 25, 26, 31, 35, 40.
- Perceptual distortion (10 items): 5, 20, 22, 27, 32, 36, 43, 44, 45.
- Cognitive Disorganization (9 items): 2, 8, 10, 13, 28, 30, 34, 37, 46, 47.
- Anhedonia (7 items): 1, 6, 9, 15, 18, 24, 39.
- Mania (6 items): 3, 16, 21, 29, 41, 48.
- Paranoia (8 items): 7, 11, 14 17, 23, 33, 38, 42.

4.4 Schedule of Study Visits

The schedule of Study Visits for each intervention group and time point, and the list of clinical and behavioral measures occurring at each of these visits are provided in tabular format in the section below.

Figures showing the workflows and timing of research procedures for each of the treatment groups are provided in the Appendix at the end of this document.

4.4.1 Administration Timepoints and Schedule of Clinical and Behavioral Assessments

Table 1. Administration timepoints and assessment measures for serial ketamine patients

	Consult	Baseline	Infusion #1	24-hr post 1st Infusion	Infusion #2	Infusion #3	Infusion #4	24-hr post 4th Infusion	Follow-up
HDRS	X	X		X				X	X
SCID-5	X								
MRI		X		X				X	X
QIDS		X	X	X	X	X	X	X	X
DASS-14		X		X				X	X
SHAPS		X		X				X	X
AES		X		X				X	X
BIS/BAS		X		X				X	X
MCTQ		X							
PSQI		X		X				X	X
Fagerstrom		X							
WHODAS		X							
Comorbidity		X							
Handedness		X							
NIHT		X		X				X	X
AMT		X		X				X	X
CADSS			X		X	X	X		
GASE			X		X	X	X		
PSI			X		X	X	X		

A subsample of patients was assessed after the 1st infusion, and at 5-weeks after the 4th infusion

Table 2. Administration timepoints and assessment measures for ECT patients

	Consult/ Baseline	Post-Treatment Assessment	Follow-Up
HDRS	X	X	X
SCID-5	X		
MRI	X	X	X
QIDS	X	X	X
DASS-14	X	X	X
SHAPS	X	X	X
AES	X	X	X
BIS/BAS	X	X	X

MCTQ (Chronotype)	X		
PSQI	X	X	X
Fagerstrom	X		
WHODAS-12	X		
Comorbidity	X		
Handedness	X		
NIHT	X	X	X
AMT	X	X	X

Table 3. Administration timepoints of assessment measures for the TSD patients

	Consult	Baseline (Pre-TSD)	TSD	Post-TSD Assessment	Follow-Up
HDRS	X	X		X	
SCID-5	X				
MRI		X		X	
QIDS		X	X		X
DASS-14		X		X	
SHAPS		X		X	
AES		X		X	
BIS/BAS		X		X	
PSQI		X			X
MCTQ		X			
Fagerstrom		X			
WHODAS		X			
Comorbidity		X			
Handedness		X			
NIHT		X		X	
AMT		X		X	

Patients and a subsample of control participants received TSD

Table 4. Administration timepoints and assessment measures for controls

	Consult	Baseline	Follow-Up
HDRS		X	X
SCID-5	X		
MRI		X	X
QIDS		X	X
DASS-14		X	X
SHAPS		X	X
AES		X	X
BIS/BAS		X	X
MCTQ		X	
PSQI		X	X

Fagerstrom		X	
WHODAS		X	
Comorbidity		X	
Handedness		X	
NIHT		X	X
AMT		X	X

A subsample of controls received follow-up/repeat assessments without any intervention

4.5 MRI Procedures

All imaging data for this CRHD project were collected on Siemens MAGNETOM Prisma 3T scanner located at the UCLA ALBMC using a 32-channel head coil. MRI sequences were *identical* to those of the Lifespan HCP-Aging (HCP-A) study[5,6], see https://www.humanconnectome.org/study/hcp-lifespan-aging, for which the UCLA ALBMC also served as an HCP-A data acquisition site. However, for this CRHD, the imaging protocols were varied slightly by reducing the acquisition time (2-runs rather than 4-runs) and number of volumes for resting state fMRI in patients with depression and non-depressed controls scanned at repeat time points. Controls scanned at baseline only included all 4-runs of resting state fMRI.

The protocol also differed by including only one functional imaging task, the *Conditioned Approach Response Inhibition Task (CARIT)*[29], that overlapped with HCP-A. However, the protocol instead added a different functional imaging task, the *Emotion Recognition Task*[30], not used in HCP-A, though employed in other CRHD projects of depression and anxiety[1]. Although functional tasks differed, BOLD sequence parameters remained identical to the HCP-A project.

The MRI data acquisition protocol lasted 75-90 minutes, depending on whether 4 or 2 sets of resting state scans were acquired (see Table 5. below)

4.5.1 Standard Operating Procedures for MRI Acquisition

SOPs developed for the HCP Lifespan projects for scanner set-up and subject positioning, including physiological monitoring, headphone noise cancellation, motion monitoring etc., as well as the order of acquisition were followed for the MRI data collected in this CRHD project.

4.5.1.1 Physiological equipment setup (respiration belt and heart rate monitor)

The Respiration band was placed on the center of the torso at the location of maximum movement during breath. A suitable alternative position was with the top of the respiration band just under the bottom of the rib cage. The band was fastened snugly with the strap. The Respiratory pillow was positioned under the respiration band so that it was snug between the torso and the band.

The heart rate monitor/pulse oximeter was placed on the tip of the left ring finger (primary position), so that the red light shone directly on the nail. A suitable alternative was the index finger of the left hand. Hands were covered with a cloth/blanket/pillowcase for warmth and to keep light out.

The participant was reminded of the importance of keeping their hand still for pulse oximeter measurements, and to breathe normally for respiratory measurements during the scan. The left hand and arm were placed at the participant's side on scanner table. Alternatively, for larger participants, the hand could be placed on the upper thigh.

Study staff ensured high quality physio traces (clear peaks and troughs, without flattening out at the ceiling or floor) before moving the participant into the bore of the magnet. Staff observed at least 10 heart beats after complete preparation of the participant before moving the table to laser positioning.

4.5.1.2 Positioning

Cushions and sponges were used to ensure the participant's head remained stable and that they were comfortable. A leg pillow was also used to promote participant comfort and minimize chances of movement during scanning.

Participants were instructed to remain as still as possible for the duration of the scan. Images were QC'd in real-time by study staff, and if any problems were observed (e.g., slice missingness, dropout, participant movement), these scans were reacquired.

4.5.1.3 Motion

In addition to visually monitoring subjects and images as data were acquired, Framewise Integrated Real-time MRI Monitoring (FIRMM) software (https://nousimaging.com) was used to provide real-time monitoring of subject motion during functional imaging sequences. In accordance with HCP SOPs, scans were stopped and subjects reinstructed to remain still if their motion was above <0.4 mm in the first 60 sec. If motion was <0.3 mm, subjects were reinstructed to try and remain still for subsequent scans.

Prospective motion correction during structural T1- and T2-weighted scans was achieved using volumetric navigators (vNavs).[31]

4.5.1.4 Scanner Noise

All participants were instructed to wear foam earplugs and were fitted with Siemens noise-attenuating headphones for the duration of the scan. This provided protection from possible hearing injury from the acoustic noise generated by the scanner.

Active noise cancellation was also used for functional imaging. Here, a short BOLD sequence was run to calibrate the headphones to not transmit unwanted scanner noise.

4.5.1.5 Stimulation equipment

The Avotec back projector system was used to display stimulation tasks using standard protocols. Prescription lenses were provided if necessary. Button presses were recorded using a Current Designs Response box.

Psychopy (v2) software (https://www.psychopy.org) was used to administer each of the functional tasks in the scanner. The ability of subjects to read the task instructions and record button presses was checked before the start of each scan. Participant responses were monitored throughout the scan.

4.5.2 Imaging Protocol

Imaging protocols included structural MRI (T1 and T2-weighted scans), resting-state (rfMRI) and task (tfMRI) functional MRI, diffusion (dMRI) and perfusion (arterial spin labelling (ASL)) MRI. As noted above, the sequences used for each of these imaging modalities were identical to those employed for the HCP-A Lifespan project[5], for which data was also collected at the UCLA site. The parameters for each of these sequences are provided as an Appendix for each treatment cohort and controls at the end of this document. In summary, MRI protocols included:

- T1w (MPRAGE) and T2w (SPACE) structural scans of 0.8 mm isotropic resolution[5], with real-time motion correction[31].
- Resting state fMRI (rfMRI) of 2mm isotropic resolution, multiband (MB) acceleration factor of 8, TR 800ms, acquired twice: once with AP and once with PA phase encoding[5,32].
- Diffusion MRI (dMRI) 1.5mm isotropic, MB acceleration factor of 4, 185 directions across two shells (b=1500 and 3000 s/mm2) with two runs including AP (92 directions) and PA (93 directions) phase encoding[5].
- Task fMRI (tfMRI) was used to measure functional correlates of behavior. In this CHRD project, these tasks focused on inhibitory control and emotion described in more detail in section 4.4.2.1:
  - Conditioned Approach Response Inhibition Task (CARIT) with the same sequence parameters as rfMRI acquired in a single run with PA phase encoding[29,33].
  - Emotion Recognition Task (Face-matching) with the same sequence parameters as rfMRI acquired in two runs: once with AP and once with PA phase encoding[30].
- Pseudo-continuous ASL (pCASL) - MB acceleration factor = 6, 60 slices with an isotropic resolution of 2.5 mm, TR/TE= 3.58/19 ms, labeling duration = 1500 ms[5,34].

4.5.2.1 Example MRI session

Table 5. Example scan session performed at each time point for patients and controls

Order	Sequence	Acquisition time (hrs:min:sec)	Notes
1	Localizer	0:00:09	Set of HCP localizers
2	AAHScout	0:00:14	
3	Localizer_aligned	0:00:21	
4	SpinEchoFieldMap_AP	0:00:09	BOLD Field maps with AP and PA phase encoding
5	SpinEchoFieldMap_PA	0:00:09	
6	Cal_800TR	0:00:30	Calibration of noise cancelling headphones
7	rfMRI_REST_AP	0:06:41	rfMRI with AP and PA phase encoding
8	rfMRI_REST_PA	0:06:41	
9	T1w_setter	0:00:02	T1 navigator set for motion correction
10	T1w_MPR_vNav_4e	0:08:22	T1 scan (multi-echo MPRAGE)
11	T2w_setter	0:00:03	T2 navigator set for motion correction
12	T2w_SPC_vNav	0:06:35	Motion correction navigator
13	SpinEchoFieldMap_AP	0:00:09	*BOLD field maps with AP and PA phase encoding
14	SpinEchoFieldMap_PA	0:00:09	
15	rfMRI_REST_AP	0:06:41	*rfMRI with AP and PA phase encoding
16	rfMRI_REST_PA	0:06:41	
Optional Break			
	Localizer	0:00:09	Localizers only repeated if break requested
	AAHScout	0:00:14	
	Localizer_aligned	0:00:21	
17	dMRI_dir98_AP	0:05:38	dMRI with AP and PA phase encoding
18	dMRI_dir98_PA	0:05:38	
19	dMRI_dir99_AP	0:05:42	dMRI with AP and PA phase encoding

20	dMRI_dir99_PA	0:05:42	
21	SpinEchoFieldMap_AP	0:00:33	BOLD field maps with AP and PA phase encoding
22	SpinEchoFieldMap_PA	0:00:33	
23	tfMRI_CARIT_PA	0:04:11	tMRI – CARIT with PA phase encoding
24	tfMRI_FACEMATCHING_PA	0:04:41	tfMRI – Emotion Recognition Task with AP and PA encoding
25	tfMRI_FACEMATCHING_AP	0:04:41	
26	PCASLhr_SpinEchoFieldMap_AP	0:00:09	ASL field maps with AP and PA phase encoding
27	PCASLhr_SpinEchoFieldMap_PA	0:00:09	
28	mbPCASL_PA	0:05:29	pCASL

** A 2nd set of field maps and rfMRI was only acquired in controls scanned at baseline without repeat assessment*

Note, that only controls scanned at a single time point (baseline) completed 4 runs of resting-state fMRI; all patients completed only 2 runs of resting state fMRI. This was done to reduce the burden of imaging time for patients with the rationale that image volumes may be averaged across time points for the purpose of functional segmentation even though longitudinal analyses compare time points separately.

The Arterial Spin Labelling functional imaging sequence was not immediately available at the start of the study, and thus this sequence is missing for the first enrolled subjects (please see the **Completeness CSV** for this release available in the PDC 1.0 Documentation).

Other sequences in the protocol for particular subjects/sessions may be missing from the database due to QC issues, or because a subject terminated the scan early (the **Completeness CSV** details all data available or not-available for specific subjects).

4.5.2.2 Description of tfMRI: Conditioned Approach Response Inhibition Task (CARIT)

The Conditioned Approach Response Inhibition Task (CARIT) measures inhibitory control processes. During the task, participants view shape stimuli and are instructed to press a button as quickly as possible ("Go") to some shapes and withhold button responses (NoGo) for other shapes[29,33]. This version of the CARIT task is identical to that of the HCP-A Lifespan project[6]. The primary behavioral outcomes of this task are number of successful response inhibitions and the reaction times to each trial. Fig 3 (modified from Sahib et al., 2020[29]) provides a graphical illustration of CARIT stimuli and average brain activation maps for the NoGo>Go and Go>NoGo contrasts for patients receiving ketamine treatment and controls included in this project.

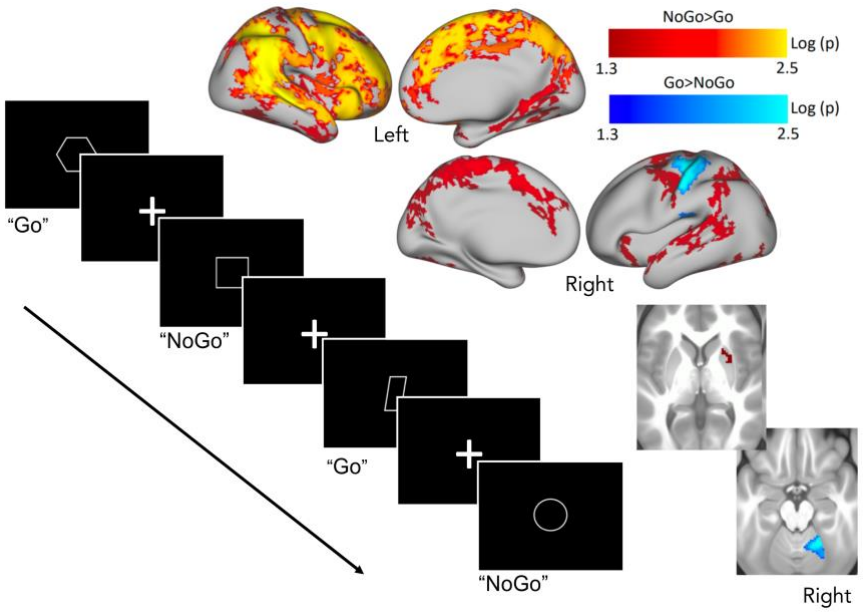


Fig 3. CARIT (Go/NGo) fMRI task showing stimulus conditions. Right: Mean activation maps for patients in the ketamine group at baseline and controls for the NoGo>Go contrast (hot colormap) and the Go>NoGo contrast (cool colormap). Images are thresholded at log(p) >1.3, which corresponds to $p < 0.05$, FWE (TFCE) corrected across grayordinates. Adapted from Sahib et al. 2020[29].

4.5.2.3 Description of tfMRI: Emotion Recognition Task (Face-matching)

This task consisted of a validated face-matching blocked paradigm[35], similar to the HCP Young Adult face-matching task[36] (EMOTION task) and adapted from Hariri et al. 2002[37]. This version of the task included faces that exhibit fearful, happy, or neutral emotions, and objects (fruits or vegetables). During this task, participants selected which of two images displayed at the bottom of the screen matched a target image displayed at the top of the screen using a button box. Fig 4 (adapted from Loureiro et al.,[30]) shows the four stimulus conditions of this task and average brain activation for the All emotion faces > objects contrast in patients with depression and control subjects participating in this study.

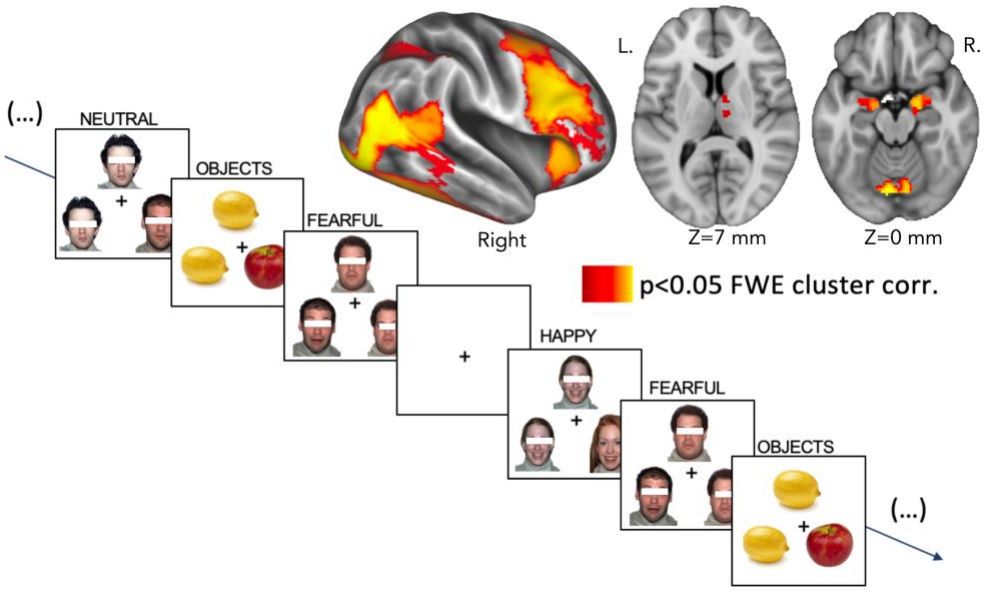


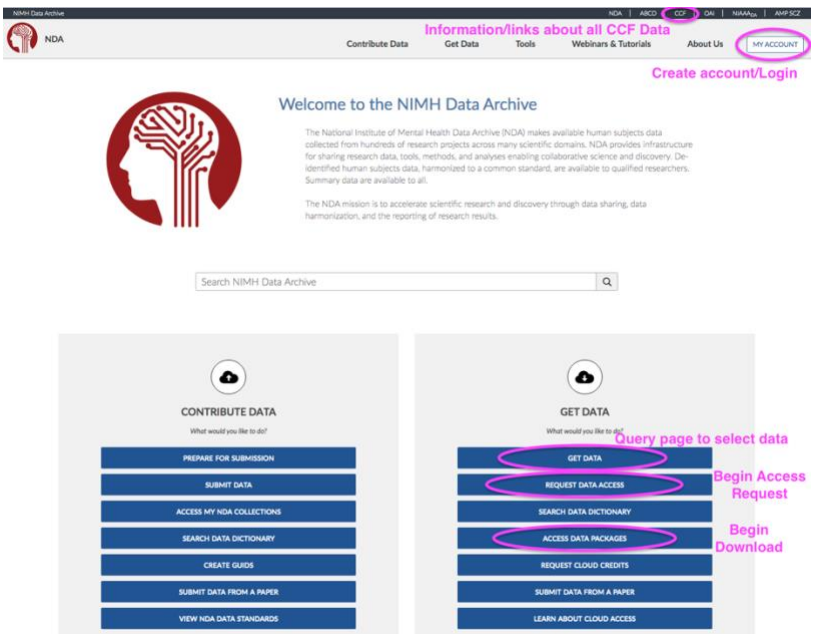
Fig 4. Emotion Recognition fMRI task showing an example of the four stimulus conditions, top right: mean activation map of the faces > objects contrast from one sample t-test of both MDD patients in the ketamine and ECT groups at baseline and controls adapted from Loureiro et al. 2020[30].

5. DATA RELEASE

5.2 Getting Data and using NDA

5.2.1 Requesting Access to NDA

Connectomes Related to Human Disease (CRHD) projects like PDC, HCP-EP, BANDA, and the Lifespan HCP (Aging & Development) projects that are managed and data processed by the Connectome Coordination Facility (CCF) are being released through the NIMH Data Archive (NDA), a data repository funded by the National Institutes of Health (NIH) and are currently only being shared through that platform (not on the cloud or other data sharing platforms).



Requesting NDA access is a multistep process that may take some time, possibly a few weeks, to gather the necessary information and signatures, especially if you are at an institution that must establish the eligibility requirements. Full instructions for obtaining access on NDA, including screenshots of the process, are available in the Lifespan HCP 2.0 Release Data Access & Download Instructions.

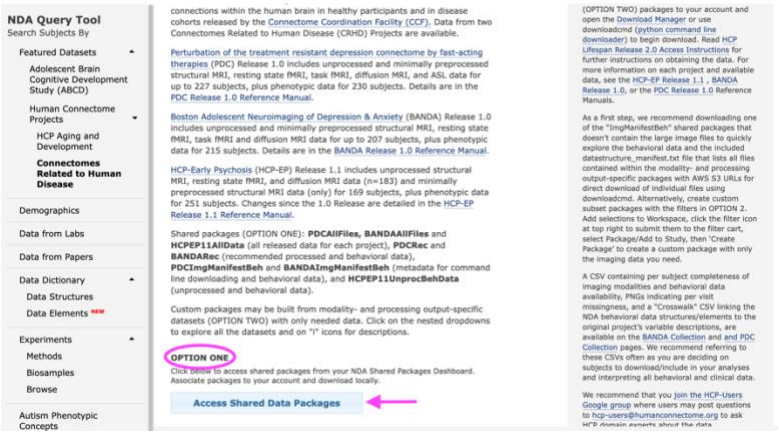
Once approved, access is valid for one full year. To maintain access, a renewal request should be submitted through the same process.

5.2.2 Selecting Data for Download

To obtain data from the Perturbation of the Depression Connectome Release 1.0, go to the Connectomes Related to Human Disease Featured Datasets query page. You can also get to this page by selecting "Get Data" from the NDA home page (pictured right), then selecting "Human Connectome Projects > Connectomes Related to Human Disease" at the top left of the query page.
On the Connectomes Related to Human Disease Featured Datasets query page, the user has two options for accessing the PDC data (scroll down to view options one and two). Read through the next section and choose the one that best fits your needs.

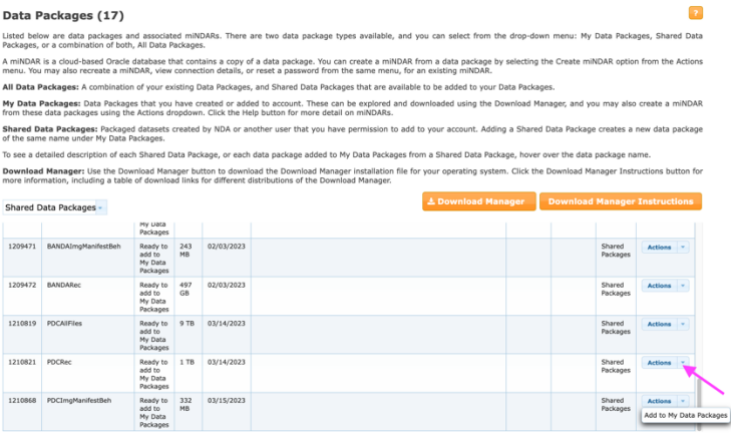
5.2.2.1 OPTION ONE

OPTION ONE accesses 3 premade, Perturbations of Depression Connectome (PDC) Release 1.0 shared data packages that we recommend as a starting point for download for many users. The **PDCAllData** package contains all released data, **PDCRec** contains recommended processed imaging data (structural, rfMRI, tfMRI, diffusion), and **PDCImgManifestBeh** contains preprocessed and unprocessed imaging metadata (no imaging data files), including the datastructure_manifest.txt file containing AWS S3 URLs for all released data files useful for command line downloading of specific files of interest. All 3 packages contain the full released clinical and behavioral data.



Click on the "Access Shared Data Packages" button (pink arrow) to take you to your Data Packages page.

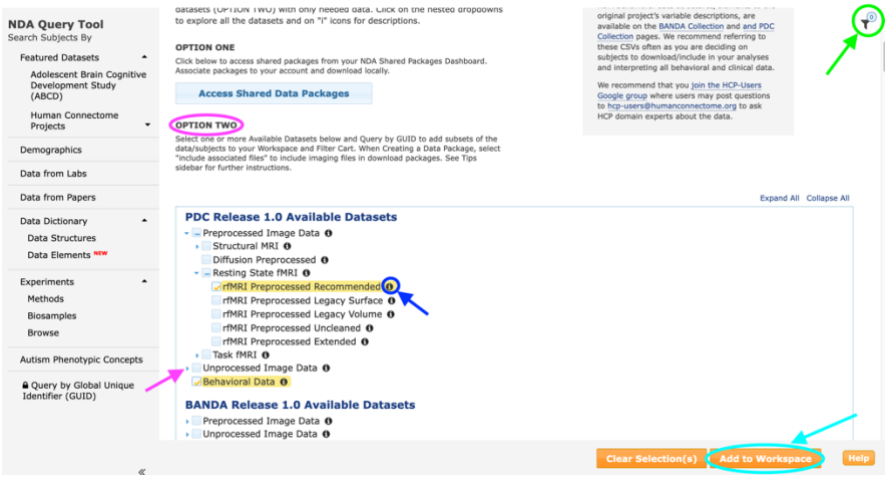
Scroll down to the PDC packages at the bottom of the list. In the Actions column in the row of the package you are interested in, select "Add to My Data Packages" (pink arrow). It will take some time (seconds to several minutes depending on size) to add the package to your account and there should be a notification at the top of the page when it is complete. In the meantime, you can proceed with downloading and setting up the NDA Download Manager or nda-tools for downloading on the command line. Full instructions for using these download options are available in the Lifespan HCP 2.0 Release Data Access & Download Instructions.



5.2.2.2 OPTION TWO

OPTION TWO allows the user to select modality- and processing output-specific "HCP-style package" filters to access part of the released data by clicking the nested dropdown options under PDC Release 1.0 Available Datasets.

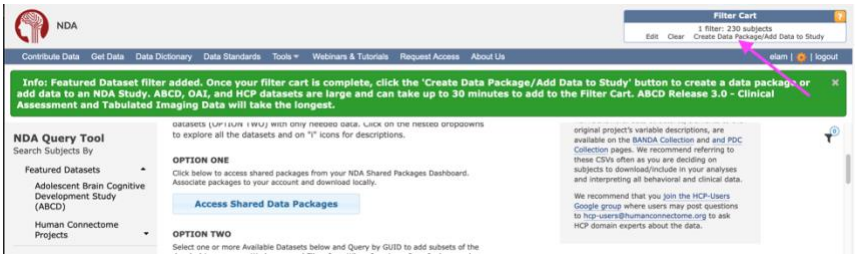
On the Connectomes Related to Human Disease Featured Datasets query page, under OPTION TWO, click the triangles next to the data types to reveal all the subset options (pink arrow). Click the black "i" information buttons (blue arrow) to see a description of the subset package.
Select the checkboxes of the subsets of the data you are interested in and click the "Add to Workspace" button at the bottom of the page (cyan arrow).



Note: The OPTION TWO subset package filters for data from all released subjects and are additive (if you make more than one selection), so total data sizes may become large. If you are interested in downloading one or a few subjects, see Filtering by Subjects in the Lifespan HCP 2.0 Release Data Access & Download Instructions.

Click on the Filter funnel icon at the top right (green arrow) showing the number of filters you added. This will show your Workspace, click "Submit to Filter Cart" at the bottom. It can take several minutes to update the Filter Cart at the top right.

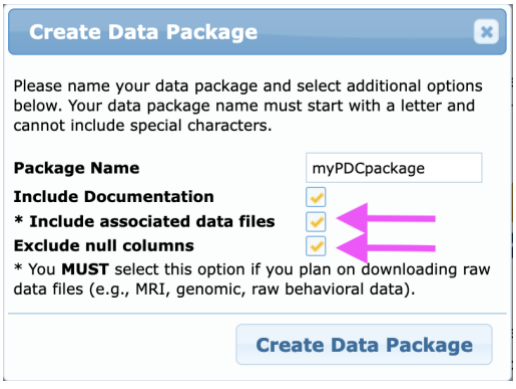
When finished, click on "Create Data Package/Add to Study" (pink arrow) at the bottom of the Filter Cart box at the top right.



On the Data Packaging page, you'll see the data you selected listed in NDA Data Structure categories (mostly useful for Behavioral data, click on the "i" buttons to see a tabular preview of the data).

Click the "Create Data Package" button to create your custom package. Enter a Package Name, be sure to click the "Include associated data files" checkbox (MRI data are considered associated data files), and "Exclude null columns" (pink arrows), so the behavioral data will not have extraneous columns for unused variables.

Click "Create Data Package". The process of creating the package will take several minutes and can be tracked from your Packages Dashboard, with "My Packages" selected at the top left. You may need to refresh the page to see the status change.



While you are waiting, follow the instructions in the Lifespan HCP 2.0 Release Data Access & Download Instructions to download the NDA Download Manager or command line download tools. You can also track package creation within the NDA Download Manager GUI by clicking the Reload Packages button until your package is listed as ready to download.

5.2.3 Files and Directory Structure

The user may choose to download the MRI unprocessed or preprocessed data and the behavioral data by selecting prepackaged data or choose to create their own custom package as described above.

The data package will download to the Save To: location on your file system with the top directory name matching the package name (<Package_YourPkgNumber>, or, e.g., Package_1210439).

If your package contains Minimally Preprocessed Image Data, and Unprocessed Image Data, the high-level <Package_YourPkgNumber> directory will contain:

fmriresults01/	Preprocessed data
fmriresults01.txt	Info on preprocessing pipelines run (per subject)
imagingcollection01/	Unprocessed data
imagingcollection01.txt	Listing of per subject data (by modality) in collection
md5_values.txt	md5 checksums for download verification
package_info.txt	Info on NDA filters used to create package
README.pdf	automatic README from NDA

We are using the NDA data structures fmriresults01 and imagingcollection01 (full directory structure described in Filenames and Directory Structure Appendix available from the PDC 1.0 Documentation page) to organize the preprocessed and unprocessed, respectively, per subject data into the same directory structure as that of previously released HCP Young Adult data, so that it is compatible with the expected inputs and outputs of processing through the HCP Pipelines.

The fmriresults01/ directory contains the preprocessed data for all modalities for the subjects available.
The imagingcollection01/ directory contains unprocessed data of all modalities.

Under these two directories, are high level <SubjectID_{Session#}_MR>, directories. We have organized the data into per subject, unprocessed and processed "packages" as was done for the HCP Young Adult Study in the directory structure output by and required for input to the HCP pipelines. When you download CCF data (including PDC data) from NDA it will be in this HCP-style file structure.

5.3 Behavioral Data Structures

Behavioral and clinical measures were mapped to the NDA behavioral data structures listed below. If you include Behavioral data in your download package, tab-delimited text files for all Perturbation of Depression Connectome behavioral structures will be included in the <Package_YourPkgNumber>/ directory (e.g. er4001.txt).

NDA Structure **Measure Name**

ndar_subject01	Research Subject
apath01	Apathy Evaluation Scale
bisbas01	Behavioral Inhibition Scale/Behavioral Activation Scale
dass01	Depression Anxiety Stress Scales
dccs01	Dimensional Change Card Sort Test (DCCS)
edinburgh_hand01	Edinburgh Handedness Inventory
er4001	Penn Emotion Recognition Task
fagerstrom01	Fagerstrom Test for Nicotine Dependence
flanker01	Flanker Task
hrsd01	Hamilton Depression Rating Scale
lswmt01	NIH Toolbox List Sorting Working Memory Test
mctq01	Munich ChronoType Questionnaire (empty file)
orrt01	NIH Toolbox Oral Reading Recognition Test
pcps01	Pattern Comparison Processing Speed
psm01	Picture Sequence Memory Test
psqi01	Pittsburgh Sleep Quality Index
qids01	Quick Inventory of Depressive Symptomatology
sacq01	Comorbidity Questionnaire (National Network of Depression Centers)
shaps01	Snaith-Hamilton Pleasure Scale
tpvt01	NIH Toolbox Picture Vocabulary Test
who01	World Health Organization Disability Assessment Schedule

5.4 Additional Documentation:

Filenames and Directory Structure Appendix: Listing of files and directory structure of imaging data packages available for download.

Completeness document:

PDC_1.0_Release_Completeness.csv: Overview of available behavioral and imaging data for all subjects collected at all time points (visits 1-4).

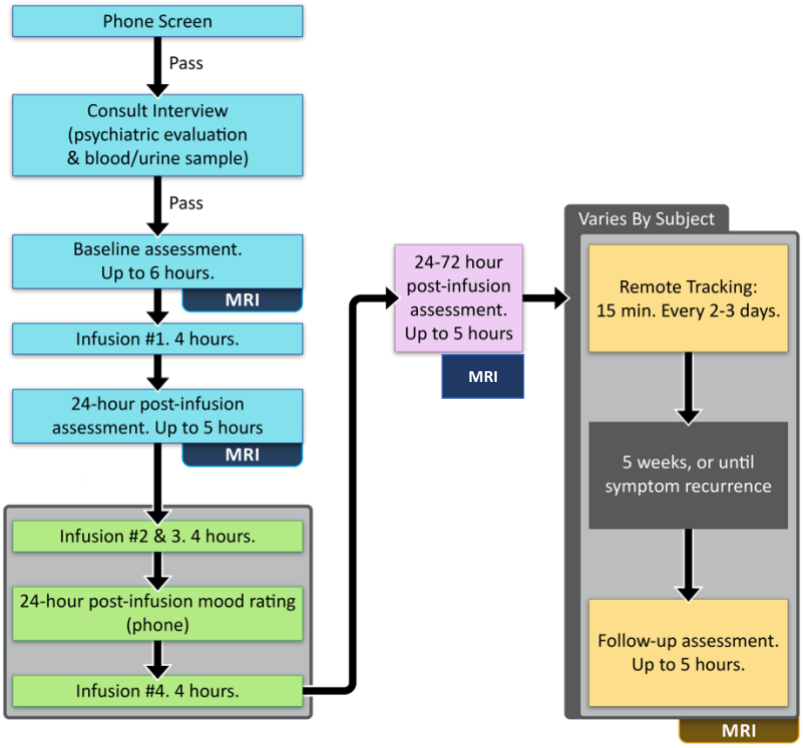
Crosswalk document:

PDC_1.0_Release_Crosswalk.xlsx: Contains information about mapping of REDCap variables to NDA elements for all available behavioral, neurocognitive, and demographic measures.

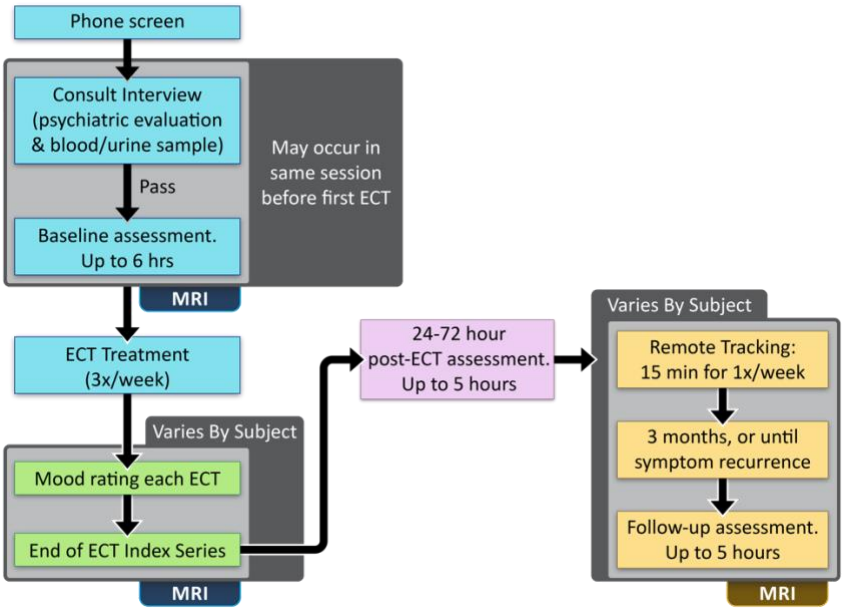
6. APPENDICES

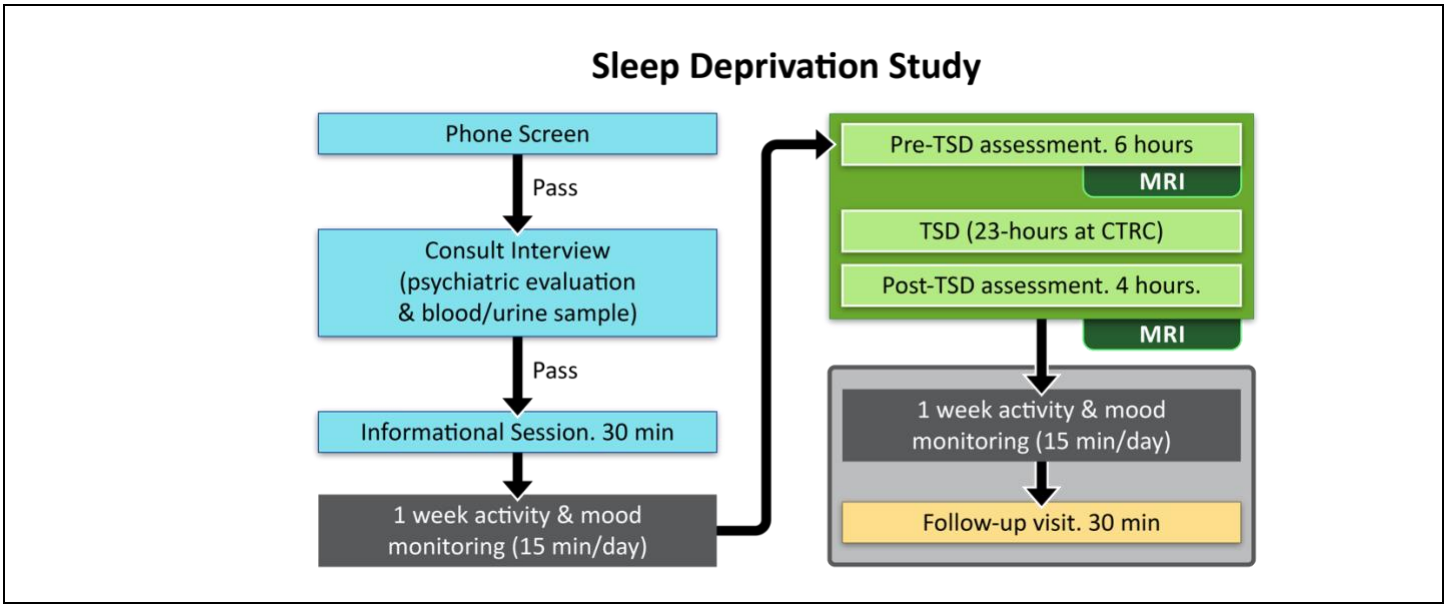
Workflows showing the schedule and timing of research procedures for each of the treatment group are illustrated graphically below.

Serial Ketamine Study



ECT Study




Sleep Deprivation Study
Phone Screen
Pass
Consult Interview
(psychiatric evaluation
& blood/urine sample)
Pass
Informational Session. 30 min
1 week activity & mood
monitoring (15 min/day)
Pre-TSD assessment. 6 hours
MRI
TSD (23-hours at CTRC)
Post-TSD assessment. 4 hours.
MRI
1 week activity & mood
monitoring (15 min/day)
Follow-up visit. 30 min

7. REFERENCES

1. Tozzi L, Anene ET, Gotlib IH, Wintermark M, Kerr AB, Wu H, Seok D, Narr KL, Sheline YI, Whitfield-Gabrieli S, Williams LM. Convergence, preliminary findings and future directions across the four human connectome projects investigating mood and anxiety disorders. Neuroimage. Elsevier BV; 2021 Oct;(118694):118694.

2. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M, STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006 Jan;163(1):28–40. PMID: 16390886

3. Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68 Suppl 8:17–25. PMID: 17640154

4. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry. 2001;62 Suppl 16:10–17. PMID: 11480879

5. Harms MP, Somerville LH, Ances BM, Andersson J, Barch DM, Bastiani M, Bookheimer SY, Brown TB, Buckner RL, Burgess GC, Coalson TS, Chappell MA, Dapretto M, Douaud G, Fischl B, Glasser MF, Greve DN, Hodge C, Jamison KW, Jbabdi S, Kandala S, Li X, Mair RW, Mangia S, Marcus D, Mascali D, Moeller S, Nichols TE, Robinson EC, Salat DH, Smith SM, Sotiropoulos SN, Terpstra M, Thomas KM, Tisdall MD, Ugurbil K, van der Kouwe A, Woods RP, Zöllei L, Van Essen DC, Yacoub E. Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. Neuroimage. Elsevier BV; 2018 Dec;183:972–984. PMCID: PMC6484842

6. Bookheimer SY, Salat DH, Terpstra M, Ances BM, Barch DM, Buckner RL, Burgess GC, Curtiss SW, Diaz-Santos M, Elam JS, Fischl B, Greve DN, Hagy HA, Harms MP, Hatch OM, Hedden T, Hodge C, Japardi KC, Kuhn TP, Ly TK, Smith SM, Somerville LH, Uğurbil K, van der Kouwe A, Van Essen D, Woods RP, Yacoub E. The lifespan Human Connectome Project in aging: An overview. Neuroimage. Elsevier BV; 2019 Jan 15;185:335–348. PMCID: PMC6649668

7. Dsm-5 STRUCTUREDCLINICALINTERVIEWFOR, Mb RESEARCHVERSIONF, Jbw W, Rs K, Rl S. Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5. Research Version. Arlington, VA: American Psychiatric Association; 2015;SCID-5-RV.

8. Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ. NIH toolbox for assessment of neurological and behavioral function. Neurology. Ovid Technologies (Wolters Kluwer Health); 2013 Mar 12;80(11 Suppl 3):S2-6. PMCID: PMC3662335

9. Hodes RJ, Insel TR, Landis SC, NIH Blueprint for Neuroscience Research. The NIH toolbox: setting a standard for biomedical research. Neurology. Ovid Technologies (Wolters Kluwer Health); 2013 Mar 12;80(11 Suppl 3):S1. PMCID: PMC3662338

10. Gur RC, Richard J, Hughett P, Calkins ME, Macy L, Bilker WB, Brensinger C, Gur RE. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. J Neurosci Methods. Elsevier BV; 2010 Mar 30;187(2):254–262. PMCID: PMC2832711

11. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. J Abnorm Psychol. American Psychological Association (APA); 1986 May;95(2):144–149. PMID: 3711438

12. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. Wiley; 1967 Dec;6(4):278–296. PMID: 6080235

13. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. Elsevier BV; 2003 Sep 1;54(5):573–583. PMID: 12946886

14. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol. Wiley; 2005 Jun;44(Pt 2):227–239. PMID: 16004657

15. Osman A, Wong JL, Bagge CL, Freedenthal S, Gutierrez PM, Lozano G. The Depression Anxiety Stress Scales-21 (DASS-21): further examination of dimensions, scale reliability, and correlates. J Clin Psychol. Wiley; 2012 Dec;68(12):1322–1338. PMID: 22930477

16. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995 Jul;167(1):99–103. PMID: 7551619

17. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. J Clin Psychol. Wiley; 2006 Dec;62(12):1545–1558. PMID: 17019674

18. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J Pers Soc Psychol. American Psychological Association (APA); 1994;67(2):319–333.

19. Jones SE, Lane JM, Wood AR, van Hees VT, Tyrrell J, Beaumont RN, Jeffries AR, Dashti HS, Hillsdon M, Ruth KS, Tuke MA, Yaghootkar H, Sharp SA, Jie Y, Thompson WD, Harrison JW, Dawes A, Byrne EM, Tiemeier H, Allebrandt KV, Bowden J, Ray DW, Freathy RM, Murray A, Mazzotti DR, Gehrman PR, Lawlor DA, Frayling TM, Rutter MK, Hinds DA, Saxena R, Weedon MN. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun. Springer Science and Business Media LLC; 2019 Jan 29;10(1):343. PMCID: PMC6351539

20. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. Elsevier BV; 1989 May;28(2):193–213. PMID: 2748771

21. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K-O. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. Addiction. Wiley; 1991 Sep;86(9):1119–1127.

22. Ustün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, Saxena S, von Korff M, Pull C, WHO/NIH Joint Project. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ. WHO Press; 2010 Nov 1;88(11):815–823. PMCID: PMC2971503

23. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. Wiley; 2003 Apr 15;49(2):156–163. PMID: 12687505

24. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. Elsevier BV; 1971 Mar;9(1):97–113. PMID: 5146491

25. Marin, Biedrzycki, Firinciogullari. Apathy Evaluation Scale (AES). A Compendium of Tests, Scales and Questionnaires. Psychology Press; 2020. p. 279–283.

26. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. Wiley; 1998 Jan;11(1):125–136. PMID: 9479681

27. Gomi Y, Matsunaga S, Takai Y, Fukatsu M, Akahori T, Ono Y, Nagai T, Saito M, Baba K, Seki H. Assessment of side effects of generic injectable ritodrine hydrochloride products. Hypertens Res Pregnancy. Japan Society for the Study of Hypertension in Pregnancy; 2016;4(2):97–101.

28. Mason OJ, Morgan CJM, Stefanovic A, Curran HV. The psychotomimetic states inventory (PSI): measuring psychotic-type experiences from ketamine and cannabis. Schizophr Res. Elsevier BV; 2008 Aug;103(1–3):138–142. PMID: 18387788

29. Sahib AK, Loureiro JR, Vasavada MM, Kubicki A, Wade B, Joshi SH, Woods RP, Congdon E, Espinoza R, Narr KL. Modulation of inhibitory control networks relate to clinical response following ketamine therapy in major depression. Transl Psychiatry. Springer Science and Business Media LLC; 2020 Jul 30;10(1):260. PMCID: PMC7393172

30. Loureiro JRA, Leaver A, Vasavada M, Sahib AK, Kubicki A, Joshi S, Woods RP, Wade B, Congdon E, Espinoza R, Narr KL. Modulation of amygdala reactivity following rapidly acting interventions for major depression. Hum Brain Mapp. Wiley; 2020 May;41(7):1699–1710. PMCID: PMC7268016

31. Tisdall MD, Reuter M, Qureshi A, Buckner RL, Fischl B, van der Kouwe AJW. Prospective motion correction with volumetric navigators (vNavs) reduces the bias and variance in brain morphometry induced by subject motion. Neuroimage. Elsevier BV; 2016 Feb 15;127:11–22. PMCID: PMC4754677

32. Sahib AK, Loureiro JR, Vasavada M, Anderson C, Kubicki A, Wade B, Joshi SH, Woods RP, Congdon E, Espinoza R, Narr KL. Modulation of the functional connectome in major depressive disorder by ketamine therapy. Psychol Med. Cambridge University Press (CUP); 2020 Dec 3;1–10. PMID: 33267926

33. Loureiro J, Sahib A, Vasavada M, Kubicki A, Wade B, Joshi S, Leaver A, Woods R, Espinoza R, Narr K. Ketamine modulation of cerebro-cerebellar connectivity during response-inhibition in major depression. Biol Psychiatry. Elsevier BV; 2020 May;87(9):S301.

34. Sahib AK, Loureiro JRA, Vasavada MM, Kubicki A, Joshi SH, Wang K, Woods RP, Congdon E, Wang DJJ, Boucher ML, Espinoza R, Narr KL. Single and repeated ketamine treatment induces perfusion changes in sensory and limbic networks in major depressive disorder. Eur Neuropsychopharmacol. Elsevier BV; 2020 Apr;33:89–100. PMID: 32061453

35. Chai XJ, Hirshfeld-Becker D, Biederman J, Uchida M, Doehrmann O, Leonard JA, Salvatore J, Kenworthy T, Brown A, Kagan E, de Los Angeles C, Whitfield-Gabrieli S, Gabrieli JDE. Functional and structural brain correlates of risk for major depression in children with familial depression. NeuroImage Clin. Elsevier BV; 2015 May 21;8:398–407. PMCID: PMC4474282

36. Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, Glasser MF, Curtiss S, Dixit S, Feldt C, Nolan D, Bryant E, Hartley T, Footer O, Bjork JM, Poldrack R, Smith S, Johansen-Berg H,

Snyder AZ, Van Essen DC. Function in the human connectome: Task-fMRI and individual differences in behavior. Neuroimage. Elsevier BV; 2013 Oct;80:169–189.

37. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. Science. American Association for the Advancement of Science (AAAS); 2002 Jul 19;297(5580):400–403. PMID: 12130784