Cover Sheet

Protocol Name: Ketamine Treatment Effects on Synaptic Plasticity in Depression

Protocol NCT Number: NCT04091971

Date: September 15, 2022

Protocol Title:
Examining the effects of ketamine treatment on synaptic plasticity in depression using PET imaging

Version Date:
09/15/2022

Protocol Number:
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Research Area:
Molecular Imaging & Neuropathology

Division:
Molecular Imaging and Neuropathology

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
MIND
Within the department, what Center or group are you affiliated with, if any?
N/A

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
N/A

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Arterial Line
✓ Collection of Biological Specimens
✓ Internet-based Data Collection or Transmission
✓ Medication Trial
✓ MRI
✓ Neuropsychological Evaluation
✓ Off-label Use of Drug or Device
✓ PET/SPECT Scan
✓ Psychiatric Assessment
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes

Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Diane Goldberg Foundation
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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Depression is the leading cause of disability globally (1, 2). One-third to one-half of patients suffering from major depressive disorder (MDD) do not achieve remission even after multiple antidepressant trials (3). Ketamine is a commonly-used FDA-approved anesthetic medication that at subanesthetic doses leads to rapid antidepressant and anti-suicidal ideation effects in hours, rather than weeks, following administration. Despite these promising findings, a key limitation of ketamine treatment is that it only yields an antidepressant response in approximately 50% of those treated. The goal of this project is to A) elucidate ketamine's mechanism of action and B) identify biomarkers predicting treatment outcome to ketamine which could be used to match patients to treatment based on the likelihood of effectiveness at the individual level. Data from animal models suggests that ketamine acts by enhancing the connections between neurons through a process known as synaptic plasticity (4-7), and that these biological changes are responsible for the sustained behavioral effects of ketamine (8). A newly available tool allows us to image the density of these synaptic connections in the living brain using PET imaging with a radiotracer called [^{11}C]UCB-J, which is a marker of synaptic density. We propose to directly quantify synaptic density in depressed patients before and after a course of ketamine, to examine changes in density following treatment. In exploratory analyses, we will examine synaptic density as a mediator of the sustained antidepressant effects of ketamine and as a predictor of treatment

outcome. To study these questions, we will quantify synaptic density using PET imaging before and after a course of 4 sequential intravenous infusions of ketamine administered over a two-week period.

As a further enhancement to the specific goals of this project (A: elucidate ketamine's mechanism of action; B: identify biomarkers predicting treatment outcome to ketamine), we propose to add non-invasive and cost-effective neurophysiological measures to the study protocol. Electroencephalogram (EEG) will be obtained at baseline and after ketamine treatment during two standard paradigms (at rest with eyes open/closed, loudness-dependent auditory evoked potentials [LDAEP]) that have shown 1) predictive utility for antidepressant treatment response and 2) sensitivity to ketamine administration.

Background, Significance and Rationale

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Depression is the leading cause of disability globally (1, 2). One-third to one-half of patients suffering from major depressive disorder (MDD) do not achieve remission even after multiple antidepressant trials (3). Ketamine is a commonly-used FDA-approved anesthetic and non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist. Recent randomized trials demonstrate that subanesthetic doses of ketamine lead to rapid antidepressant and anti-suicidal ideation effects in individuals with MDD and bipolar depression (reviewed in (9)). In contrast to current FDA-approved antidepressants, ketamine exerts antidepressant effects in hours, rather than weeks, following administration. Despite these promising findings, a key limitation of ketamine treatment is that it only yields an antidepressant response in approximately 50% of those treated. In addition, ketamine's clinical utility is limited by its acute dissociative side effects, a one to two-week duration of action as monotherapy, its addictive potential, and long-term safety concerns related to cognition and interstitial cystitis (9-11). Given the profound benefit of ketamine for some individuals yet these key limitations, developing a precision medicine research strategy for ketamine's antidepressant effects could be of tremendous scientific and clinical benefit, in order to A) elucidate ketamine's mechanism of action, to advance the development of safer alternative agents and B) identify biomarkers predicting treatment outcome to ketamine, which could be used to match patients to treatment based on the likelihood of effectiveness at the individual level.

There is evidence of brain atrophy in depression: gray matter volume is reduced in the prefrontal cortex (PFC) and in the hippocampus (HC) in depressed individuals (12). Postmortem studies in depression show low expression of several genes related to synaptic function and decreased synapse number in the dorsolateral PFC (13). Chronic stress, a risk factor for depression, precipitates neuronal atrophy and dendritic spine loss in HC and PFC (14, 15). Pre-clinical work in rodents suggests that ketamine may exert antidepressant effects by reversing neuronal atrophy, specifically through the formation of new dendritic spine synapses in the brain. In rodents, ketamine induces rapid synaptogenesis via stimulation of mechanistic target of rapamycin (mTOR) and brain-derived neurotrophic factor (BDNF), leading to a reversal of chronic, stress-induced neuronal atrophy (4-7).

A recently developed research tool enables examination of synaptic density *in vivo* in humans. [^{11}C]UCB-J is a PET radiotracer that is specific for synaptic vesicle glycoprotein 2A (SV2A) (16, 17), providing a quantitative measure of synaptic density *in vivo* in the brain in humans. A recent PET imaging pilot study identified low [^{11}C]UCB-J binding in the PFC of individuals with current MDD as compared to healthy volunteers, providing early evidence that this synaptic density biomarker may quantify a disease-relevant process in depression (18). Furthermore, PET imaging with [^{11}C]UCB-J displays outstanding test-retest reliability, with absolute test-retest variability of only 4-5% in brain regions of interest in this study (19), making it an outstanding tool for longitudinal studies of the effects of treatment interventions. We therefore propose to directly quantify synaptic density in depressed patients to investigate whether it is increased by treatment with ketamine in a regionally-specific manner. Moreover, we will examine synaptic density as a mediator of the sustained antidepressant effects of ketamine and as a predictor of treatment outcome. We will quantify synaptic density using PET imaging before and after a course of 4 sequential intravenous infusions of ketamine administered over a two-week period.

Two oscillatory measures derived from resting EEG, midfrontal (anterior cingulate) theta and posterior (occipital-parietal) alpha, have been identified as putative EEG biomarkers of treatment outcome in depression (e.g., Pizzagalli et al., 2001, 2018; Smith et al., 2019; Tenke et al., 2011). Studies of ketamine in healthy participants and MDD patients also highlight the important role of these frontal and posterior regions. For example, ketamine administration in healthy participants increased activation in frontal brain regions (ACC, dlPFC, mPFC), including specific increases in ventral ACC theta activity and decreases at posterior regions (PCC, TPJ; McMillan et al., 2019; Mueller et al., 2019; see Curic et al., 2019). Studies of post-ketamine effects in MDD patients showed increases and normalization of dorsal-frontal PFC activity (Abdallah et al., 2017; Ionescu et al., 2019) and decreases of hyperactive bottom-up salience-related regions such as rACC and INS (Reed et al., 2019). Further, resting EEG studies of ketamine showed decreases in dominant (posterior-parietal) alpha oscillations and increases of slower (theta) and faster (gamma) oscillations, that is, increased frontal theta, decreased parietal-occipital alpha and global beta, and increases in global gamma (McMillan et al., 2019; Muthukumaraswamy et al., 2015; Vlisides et al., 2018; Zacharias et al., 2019).

Data from animal models suggest that the LDAEP slope of the auditory N1/P2 amplitude (monotonic increase with increasing intensity) is indicative of serotonergic function (e.g., Hegerl et al., 1994, 2001), and several LDAEP studies reported a differential prediction of clinical response to serotonergic versus noradrenegric and placebo treatment (Gallinat et al., 2000; Lee et al., 2015; Mulert et al., 2002; Paige et al., 1994, 1995). Moreover, NMDA receptor blockade in monkeys blunted the LDAEP response, suggesting that the NMDA antagonist ketamine will likewise result in a blunted LDAEP response (i.e., shallower slope; Teichert, 2017). Use of the LDAEP in this project will increase knowledge regarding ERP studies of ketamine in humans, which revealed a general pattern of reduced cognitive ERPs (N2, P2, P3, MMN) but equivocal findings regarding ketamine-related increases and decreases in sensory ERPs (P50, P1, N1; Rosburg et al., 2016; Rosch et al., 2019; Schwertner et al., 2018).

Brain connectivity studies related to ketamine in healthy humans showed decreased functional connectivity (FC) across frontal, parietal, insular, and occipital cortices, including decreased within-occipital alpha FC, and increases in delta and theta frontal-occipital FC as well

as low beta FC between frontal and precuneus/insula regions (Forsyth et al., 2019). After ketamine, MDD patients show decreased dlPFC-ACC connectivity as well as increased within-frontal, PFC-PCC and DMN-Salience connectivity (Abdallah et al., 2017; Evans et al., 2018; Fleming et al., 2019). Related work with healthy humans during ketamine showed decreased FC across frontal, parietal, insular, and occipital cortices, including decreased within-occipital alpha FC, and increases in delta and theta frontal-occipital FC as well as low beta FC between frontal and precuneus/insula regions (Forsyth et al., 2019). Studies examining predictors of ketamine treatment response in MDD suggested that baseline and event-related lPFC-sgACC connectivity (Gartner et al., 2019), higher rostral ACC response to fearful faces (Salvadore et al., 2009) and higher post-ketamine gamma power was associated with better antidepressant treatment response in MDD subjects with lower baseline gamma (Nugent et al., 2019).

Obtaining these EEG and ERP data will allow us to link relevant metrics to treatment response as well as to synaptic density. Specifically, changes in synaptic density should impact on functional connections between cortical regions (neuronal dynamics) and LDAEP component topographies (scalp or sensor-level radial current flow estimates; Tenke & Kayser, 2012) and tomographies (distributed inverses; Pascual-Marqui et al., 1994).

Specific Aims and Hypotheses

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AIM 1: Quantify changes in regional synaptic density in response to intravenous ketamine. We hypothesize that administration of ketamine in individuals with MDD will induce new spine synapse formation and synaptic protein synthesis, reflected by increased synaptic density in mPFC and HC as quantified by changes in V_T derived from PET imaging with [^{11}C]UCB-J performed prior to and approximately 24 hours following a course of four ketamine infusions.

AIM 2: Evaluate the relationship between sustained improvement in depressive symptoms in response to intravenous ketamine and change in ^{11}C-UCB-J binding. We hypothesize that the magnitude of the change in ^{11}C-UCB-J V_T in mPFC and HC in response to intravenous ketamine administration will correlate with clinical improvement on the Hamilton Depression Rating Scale from baseline to one week following the final ketamine infusion.

AIM 3: Examine whether baseline synaptic density in MDD-relevant brain regions as measured by PET imaging with [^{11}C]UCB-J predicts the magnitude of sustained antidepressant effects of intravenous ketamine treatment. Hypothesis: lower pre-treatment [^{11}C]UCB-J binding (V_T) in mPFC and HC will predict greater improvement in depressive symptoms assessed one week following final ketamine infusion as assessed by the Hamilton Depression Rating Scale. This aim

is based on the assumption that individuals with MDD who have particular deficits in this biological measure (regionally-specific synaptic density) will benefit most from an intervention that acts to restore such deficits.

AIM 4: Examine whether baseline EEG measures (midfrontal theta, posterior alpha, LDAEP slope) predict the magnitude of sustained antidepressant effects of intravenous ketamine treatment. Hypothesis: Greater rostral anterior cingulate cortex (rACC) theta, as identified via low resolution brain electromagnetic tomography (LORETA; e.g., Pizzagalli et al., 2001, 2018), greater posterior alpha as identified via scalp current source density (CSD; surface Laplacian) and frequency principal component analysis (fPCA; e.g., Tenke et al., 2011), and greater LDAEP will predict greater improvement in depressive symptoms assessed via the Hamilton Depression Rating Scale one week following final ketamine infusion. This aim is based on prior findings showing moderate predictive validity of these putative EEG biomarkers of treatment outcomes in depression (e.g., Pizzagalli et al., 2018; Tenke et al., 2011).

AIM 5: Examine whether pre/post ketamine treatment changes of EEG measures (midfrontal theta, posterior alpha, LDAEP slope) predict the magnitude of sustained antidepressant effects of intravenous ketamine treatment, and whether these changes are related to changes in synaptic density. Hypothesis: Ketamine treatment will reduce ERP amplitudes in general and LDAEP slope in particular; the extent of this reduction will be correlated with both reduction in depressive symptoms and increases in synaptic density. This aim is based on findings showing blunted LDAEP response after NMDA blockade (Teichart, 2017), which may be directly related to ketamine's mechanism of action resulting in its antidepressant effects.

Description of Subject Population

Sample #1

Specify subject population
Depressed adults with current MDD
Number of completers required to accomplish study aims
20
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
18-55

Gender, Racial and Ethnic Breakdown

Based on historical recruitment of depressed patients for research studies in our division, we expect the following gender and ethnic breakdown: Male (40%); Female (60%); White (67%); Black (24%); Hispanic (16%); Asian (9%).

Description of subject population

We will recruit unipolar depressed patients in a current major depressive episode. We will attempt to recruit individuals who are unmedicated in the current episode, although this will not be required for study participation. Based on studies in our clinic, subjects come from the 5 boroughs of New York City and the nearby tri-state suburbs.

Recruitment Procedures

Describe settings where recruitment will occur

Patients are recruited through advertisements and web-based recruitment tools, including Columbia's research study search engine, RecruitMe, clinician referrals, and the hospital inpatient and emergency services. These include the New York Presbyterian Hospital emergency room, referrals for inpatient and outpatient treatments from the community, a large network of referring doctors, the ECT service, the extensive outpatient depression clinics at NYSPI (e.g., Depression Evaluation Service and the Late Life Depression Center) and medical services.

How and by whom will subjects be approached and/or recruited?

Subjects will complete a preliminary phone screening with a research coordinator under the Screening Protocol (PI IRB #6879R) to determine whether most inclusion/exclusion criteria (excluding medical screening) are met. For individuals in the emergency room or on an inpatient unit, this screening may be done in person by study staff, after permission is first obtained by a treating clinician not affiliated with the study to speak with our staff about possible research participation. If participants are screened and recruited through the Emergency Room, a treating clinician will give permission for the patient to be approached, and additionally, the treating clinician will ask the patient if they are open to speaking with research staff before screening by research staff occurs.

How will the study be advertised/publicized?

Through local media, internet, mailings to clinicians, outreach to NYPH/NYSPI clinicians and other local emergency departments and clinical facilities.

Do you have ads/recruitment material requiring review at this time?

Yes

Does this study involve a clinical trial?

Yes

Please provide the NCT Registration Number

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Participants will be screened through our division's screening protocol:

IRB # 6879R: Molecular Imaging and Neuropathology Clinic Studies Initial Evaluation (PI: Elizabeth Sublette; formerly #5880R)

Participants will co-enroll in our division's umbrella protocol:

IRB #4815: Biological and neurocognitive measures for genetic studies of psychiatric populations (PI: Elizabeth Sublette)

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Depressed adults with current MDD
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion	Method of Ascertainment
1. Unipolar, major depressive episode (MDE), with 17-item Hamilton Depression Rating Scale score ≥16. Patients may be psychiatric medication- free, or if currently taking psychiatric medication, not responding adequately as evidenced by current MDE.	1. DSM-5 criteria by SCID-5 administered by trained assessors; Medication history; Clinical evaluation; Hamilton Depression Rating Scale
2. 18-55 years old	2. Interview
3. Female patients of child-bearing potential must be willing to use an acceptable form of birth control during study participation such as condoms, diaphragm, oral contraceptive pills.	3. Interview
4. Must be enrolled in IRB #4815 (PI: Sublette)	4. Interview
5. Able to provide informed consent	5. Interview. For individuals who are initially

	recruited as inpatients, an inpatient psychiatrist unaffiliated with the study will provide independent assessment of capacity.
6. Agrees to voluntary admission to an inpatient research unit at NYSPI for baseline PET/MR imaging, ketamine infusion, and repeat PET imaging	6. Interview

Create or insert table to describe the exclusion criteria and methods to ascertain them

EXCLUSION	METHOD OF ASCERTAINMENT
1. Unstable medical or neurological illness including: A) baseline hypertension (BP>140/90); B) significant history of cardiovascular illness; C) Platelet count < 80,000 cells/uL; and D) Hemoglobin < 11 g/dL for females and < 12 g/dL for males	1. Medical history, laboratory testing, all through IRB #4815
2. Significant ECG abnormality (e.g., Ventricular tachycardia, evidence of myocardial ischemia, symptomatic bradycardia, unstable tachycardia, second degree (or greater) AV block).	2. Baseline ECG
3. Pregnancy, currently lactating, or planning to conceive during the course of study participation.	3. History, baseline serum pregnancy test. Urine pregnancy tests will be repeated on the days of each MRI and PET scan, as well as one- to two-weeks after the second PET scan.
4. Diagnosis of bipolar disorder or current psychotic symptoms.	4. Clinical assessment and baseline SCID-5
5. Current or past ketamine use disorder (lifetime); any drug or alcohol use disorder within past 6 months	5. Clinical assessment, SCID, urine drug screen.
6. Inadequate understanding of English.	6. Interview
7. Prior ineffective trial of or adverse reaction to ketamine.	7. Interview
8. A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of prior head trauma and score ≥ 1.5 standard deviations below the mean on the Trailmaking A&B will be excluded from study participation.	8. Clinical interview and medical history, Trailmaking A & B as needed.
9. Metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or	9. Interview, MRI safety screening forms

interfere with the MRI scan, according to the guidelines set forth in the following reference book commonly used by neuroradiologists: "Guide to MR procedures and metallic objects," F.G. Shellock, Lippincott Williams and Wilkins NY 2001. Additionally transdermal patches will be removed during the MR study at the discretion of the investigator.	
10. Current, past, or anticipated exposure to radiation, that may include: ** -being badged for radiation exposure in the workplace -participation in nuclear medicine research protocols in the last year	10. Subjects will undergo a clinical interview during which they will be asked whether or not they have worked with radioactive substances or have been badged in the past. In addition, they are asked about any prior chemotherapy or radiation treatment and past research study participation involving radiation exposure.
11. Claustrophobia significant enough to interfere with MRI scanning	11. Interview
12. Weight that exceeds 325 lbs or inability to fit into MRI scanner	12. Weight and maximal body circumference (if necessary) as part of physical exam; visit to the MRI suite if necessary ***
13. Individuals taking prescribed opioid medication, using opioids recreationally, or taking naltrexone at the time of enrollment	13. Interview
14. Daily use of: benzodiazepine, zolpidem (Ambien), zeleplon (Sonata), or eszopiclone (Lunesta) for ≥2 weeks at time of consent	14. Interview
15. Hearing loss (> 30 dB HL) or an ear asymmetry (> 10 dB)	15. Determined using standard audiometric measures at 500, 1000, and 2000 Hz (audiogram)

** In case of previous exposure to radioactivity due to research studies, subjects will be eligible if all conditions listed below are fulfilled:
1) For any research studies performed in the past year, the injected dose and dosimetry of the radiotracer are known;
2) Except for research studies, the subject has no lifetime exposure to radiation in the workplace or in nuclear medicine procedures;

3) Adding the previous exposure to the expected exposure due to the current study will result in a yearly cumulative exposure lower than the limit defined by 21 CFR part 361.1 for research subjects (5 Rems for whole body, active blood-forming organs, lens of the eye, and gonads; 15 Rems for other organs).

*** In cases where there is a question about whether a participant's dimensions are compatible with the MRI scanner, a subject's circumference may be measured to determine if the subject's circumference is less than the MRI scanner limit, 200cm. The subject also may be brought to the

MRI center so that the MRI technologist can assess whether or not the subject will fit safely inside the MRI scanner. Metal screening and urine pregnancy testing will be done before this brief visit. Subjects who cannot safely enter the scanner will not be eligible to participate in the study.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6879R and 4815
Describe Study Consent Procedures

1. Possible participants will complete an initial phone screen with a research coordinator after providing verbal consent, through screening protocol #6879R.

2. Potentially eligible participants are scheduled for an evaluation and consent session. There, participants are given a detailed verbal explanation of screening procedures by a research staff member. Participants then give written informed consent for screening procedures (under screening protocol #6879R).

3. If eligible, based on #6879R screening, participants will be asked to sign the consent form for IRB protocol #4815 (Biological and Neuropsychological Measures for Genetic Studies of Psychiatric Populations—PI: Sublette). Participants will then be given **laboratory (blood draw)** and psychiatric examinations, performed under protocol #4815.

4. Participants will also be given a detailed verbal explanation of this study by a research MD and then will give written informed consent, if they choose to participate in the study. Subjects who are

unable to come to NYSPI for multiple visits will complete consenting via NYSPI-approved remote platforms including Webex, Zoom, or telephone. The commonest reason is that they live too far away and may fly in or take a train a long distance to participate in the study. We want to be as sure as possible they are both eligible and willing to participate before they travel a long way to come to our center.

5. A Note to File will be added to the participant's charts that documents screening and study consent discussions, signed by the consenter and dated on the day of the consent discussions.

6. Consent discussions will include informing participants of the option to reschedule if travel does not seem safe and/or the study team may offer alternative transportation, such as Uber or Lyft.

7. There will be a consent procedure note that includes that there was a discussion of risk related to COVID-19 during travel.

All screening and consenting procedures will be done remotely over a HIPAA-compliant videoconferencing software (Webex or Zoom) or telephone. We will document consent for remote clinical or research procedures, the consent discussion process will include discussion of the technology HIPAA-compliant platforms to be used and any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi.
We will use REDCap with e-signature function enabled to obtain electronic documentation of consent.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Grunebaum, Michael, MD
Lan, Martin, MD
mann, j john
Miller, Jeffrey, MD
Sublette, M, MD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?

No

Study Procedures

Describe the procedures required for this study

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- No volunteers/externs on-site during Stage 1.
- Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.
- All inpatient participants will be tested for COVID and will be determined negative for COVID prior to admission on 5 South. Testing will occur either in the ER, through an outside private laboratory or via NKI. In the latter two cases, nasal swabbing may be performed at NYSPI by trained staff and sent to these laboratories. Alternatively, COVID testing may be performed via saliva sample. COVID testing will be repeated upon admission to the inpatient unit, and within 48 hours of discharge.

Personnel and Responsibilities:

1. **Medical history**: MIND physician (covered under IRB #4815)

2. Psychiatric Interview: physician or psychologist (covered under IRB #4815)

3. Semi-structured interview: physician, psychologist or research interviewer (covered under IRB #4815)

4. Columbia PET Center staff (Elizabeth Greenstein MD, Jongho Kim MD, Akiva Mintz MD PhD) will be responsible for all aspects of the PET scans including PET tracer production under an IND held by the principal investigator.

5. The NYSPI MR Center, or in some cases other Columbia site with MR scanners, will be responsible for the conduct of MRI scans in this protocol. A MIND physician, psychologist, or research coordinator will accompany study participants to the MRI scan.

6. Administration of ketamine: MIND physician with current BLS training

7. A radiologist designated to read MRI research scans from CUMC Radiology will generate a clinical report on MRI scans

8. Open outpatient clinical treatment will be provided by MIND physicians.

9. The following people will be involved in EEG collection and analysis:

Jurgen Kayser (Co-I): EEG collection/analysis
Lidia Y.X. Wong, M.A: Lab manager/EEG RA
Tarik Bel-Bahar, Ph.D: Research Scientist with broad EEG expertise

Procedures

1. Screening

a. We will recruit inpatients or outpatients with MDD in a major depressive episode. Referrals generally come from physicians, clinics, the NYPH Emergency Department, and ads in media including the internet.

b. Participant completes phone screen, approved under IRB #6879R (which may be done in-person if in the emergency room or on an inpatient unit). If participant appears eligible based on the phone screen, they will be scheduled for a more in-depth screening visit under Screening Protocol (IRB #6879R) to determine whether inclusion/exclusion criteria (excluding medical screening) are met. Screening will occur via NYSPI-approved remote platforms including Webex, Zoom, or telephone.

c. Secure video/phone interviews: Under the procedures described in protocols #4815 and #6879R, consent forms for this protocol will be sent to the subject to be reviewed with an approved consenter at the end of the eligibility screening. Subjects will be asked to print the form prior to their eligibility screening.

d. Secure video/phone interviews: Following the interview conducted under #6879R, the consenter will review the consent form for this protocol that was emailed to the subject. Consent forms will be signed electronically by the participant and the consenter in RedCap.

e. Secure video/phone interviews: Following the procedures detailed in protocol #4815, if the consenter determines that the potential subject has suffered a serious head injury a trailmaking test (TMT) will be sent to the subject. Research staff will administer the test over secure video as described fully in protocol #4815.

f. For in-person screening procedures (which may be used with patients in the emergency room or on an inpatient unit), participant is given a detailed, verbal explanation of this study and IRB #4815 and given a copy of both consent forms.

g. Participant gives written informed consent to participate in IRB #4815 and this study.

h. Participant receives medical evaluation under IRB #4815. Genetics blood sample is also acquired under IRB #4815 (Biological and neuropsychological measures for genetic studies of psychiatric populations—PI: Sublette).

i. An electrocardiogram will be performed to evaluate any cardiovascular contraindications to research procedures.

j. Final eligibility is determined when results of laboratory tests acquired through IRB #4815 are obtained.

k. During the period between enrollment and the infusion, the treating physician will assess the patient weekly in by phone, through secure video, or in person if these options are not available, through a clinical interview and a Clinical Global Impression (CGI) scale. If concerns are noted during a telephone or secure video contact, participants may be brought in for an in-person visit. If a participant has a CGI-I >5 at any time, the treating psychiatrist will assess whether it is safe to continue research participation and will discuss with the participant the possibility of discontinuing research procedures and initiating open clinical treatment.

If after enrollment a subject refuses inpatient admission that is deemed clinically necessary by the research team they will be withdrawn from research.

2. Prior Psychiatric Medication

a. For insomnia or anxiety, PRN diphenhydramine, hydroxyzine, zolpidem, or a benzodiazepine will be permitted. The goal will be the equivalent of a maximum daily dose of lorazepam ≤2mg during the week leading to the first infusion. However, no zolpidem, eszopiclone, zaleplon, or benzodiazepine will be permitted during the 72 hours pre-infusion and during the 72 hours prior to PET imaging. Subjects who at enrollment are taking a higher equivalent benzodiazepine dose will be tapered and converted to lorazepam during the pre-infusion week. Subjects who show signs of benzodiazepine withdrawal or who cannot tolerate the 24-hours without zolpidem, eszopiclone, zaleplon, or benzodiazepine will be withdrawn from the protocol.
b. Current psychiatric medications other than benzodiazepines or the above sleep medications will be maintained at a stable dose until post-infusion treatment. Minor dose adjustments may be made pre-infusion, such as to reduce side effects.

3. Actively Suicidal Patients

a. Patients with imminent (next few days) suicidal plan or intent will only be enrolled if they agree to acute inpatient hospitalization. The independent treatment team on the inpatient research unit must agree that study participation is clinically reasonable.
b. For patients who require hospitalization because of destabilization or suicidal risk, admission to a NYSPI unit will be available. Hospitalized patients will be discharged from the

hospital when stable as judged by the inpatient staff and the treating psychiatrist as not being in imminent risk of harm to self/other.
c. A research psychiatrist will be available by telephone 24 hours a day, seven days a week. Patients requiring urgent admission will be brought to the NewYork Presbyterian/Columbia University Irving Medical Center Emergency Room by the study physician with security assistance, if needed. Non-emergent admissions will be arranged by the treating psychiatrist, if possible to 5 South or 4 Center. Patients who are deemed to require hospitalization, but who refuse hospitalization, will receive all necessary interventions such as contacting the local crisis team, family, or Emergency Medical Services.

4. Inpatient Phase.
a. To participate in the study, patients must agree to inpatient hospitalization at NYSPI (4 Center or 5 South units) throughout the period in which the following procedures occur: baseline neuroimaging (MRI and PET), ketamine infusions, and post-ketamine imaging (PET). Our goal will be for the admission to be as short as possible, but in general we anticipate that it may be on the order of 21 days, or more if clinically indicated. Patients will be evaluated by a research physician and the inpatient unit's independent clinical team and will be discharged when assessed, according to standard practice, as safe for outpatient treatment in the research clinic. Patients who need to be kept involuntarily for safety reasons will be withdrawn from research and treated clinically.

5. Pre-Infusion Research Measures
a. Baseline clinical and neuropsychological ratings (See Figure 1, attached); may be performed as inpatient or outpatient.

b. Baseline MRI imaging will take place at the New York State Psychiatric Institute on a GE SIGNA Premier 3T MRI Scanner, generally on a day prior to ketamine infusion, although it may take place after the ketamine infusion if scheduling constraints make this preferable. MR imaging will include T1-weighted structural MRI of the brain for coregistration to PET and identification of regions of interest. Resting-state functional MRI and diffusion weighted imaging acquisitions may be performed if time allows. MRI scanning time will not exceed 30 minutes. Scanning at NYSPI will occur on the GE Signa Premier 3T MRI system. A urine pregnancy test will be performed on women of child-bearing potential on the day of the MRI scan. Inpatients will be accompanied to the MRI Center by a research staff member (coordinator, psychologist or psychiatrist) who will remain in the MRI Center throughout the scan and bring them back to the inpatient unit at the completion of the scan.

c. Before the MRI occurs, participants will have the option of visiting the MRI suite and entering a mock MRI scanner. The mock scanner is identical in size to an MRI scanner but cannot take pictures of the brain. Trying out the mock MRI scanner simulation gives participants an idea of what the MRI scan will be like and may reduce their anxiety about the scan.

d. Baseline PET imaging will be performed at the Columbia PET Center prior to the first ketamine infusion, within one week prior to the first ketamine infusion; this could include scanning on the day of ketamine infusion itself prior to the infusion. PET imaging will be performed at the Columbia PET Center. SV2A will be quantified via PET with [^{11}C]UCB-J, synthesized as previously described (17). Radiotracer synthesis will occur in the radioligand laboratory at the Columbia PET Center. Baseline PET scanning will occur within one week prior to ketamine infusion. After acquisition of a low dose CT scan for attenuation correction, [^{11}C]UCB-J will be injected as an intravenous bolus (≤740mBq), and PET data acquired on a Siemens mCT Biograph over **90** minutes. A urine pregnancy test will be performed on women of child-bearing potential on the day of each PET scan.
e. Blood Analysis: A radial artery catheter will be placed prior to PET imaging for concurrent blood sampling to measure arterial input function and unmetabolized plasma fraction of [^{11}C]UCB-J using high-performance liquid chromatography. The radial artery catheter will be placed by a physician after completion of the Allen test and infiltration of the skin with 1% lidocaine. If a participant has a known allergy to lidocaine, an alternative local anesthetic may be used. Blood samples will be drawn using a combination of automated and/or manual blood sampling during the course of the PET scan. No more than 100 ml of blood will be drawn for this purpose at each of the two PET scans. In the event that a radial artery catheter cannot be placed, we may place a second intravenous catheter and perform venous blood sampling instead of arterial blood sampling.

f. After the scan is over, the participant exits the camera, the arterial and venous lines are removed, and discharge from the PET Center will be contingent upon clearance by the clinical and research staff. A member of the research team will accompany the participant back to the inpatient unit.

g. In the event that the subject needs to leave the scanner while scanning (e.g. to use the bathroom) we will perform an additional low dose CT transmission scan.

6. Ketamine Infusions.
a. Four Ketamine infusions will be administered over a two-week period with infusions occurring approximately on alternating days (such as Tues-Thurs) on each of two weeks; small variations to this schedule are allowed if necessitated by scheduling constraints.

b. Patients will eat no food for 12 hours and drink no liquids for 4 hours before each infusion. Patients will be escorted by study staff to and from the Biological Studies Unit (BSU) at NYSPI, where the infusions will occur.

c. No zolpidem or benzodiazepine will be permitted in the 24 hours prior to each ketamine infusion. We will monitor patients for signs of withdrawal, such as severe anxiety, diaphoresis, tachycardia (HR greater than 100), or hypertension (BP greater than 150/95).

d. We exclude hypertension at screening. However, patients may be anxious at the ketamine procedure, which can transiently raise BP. We will check subjects' BP approximately 1 hour pre-ketamine, and if elevated, will have the patient do relaxation exercises. If these are ineffective, the patient will be given amlodipine 5mg po. We will allow start of the infusion with BP of 150/95 or less.

e. Intravenous catheter will be placed by staff at the BSU or by a MIND physician or nurse, including Jayamole Kannamkuzhiyil.
f. Dose: Patients will receive an intravenous infusion of saline solution with ketamine hydrochloride (0.5 mg/kg; Abbott Laboratories, North Chicago, IL) over the course of approximately 40 minutes in the BSU of NYSPI, **with a study physician present at the beginning of the infusion and available throughout.**
g. Vital Signs Monitoring: During study infusion(s), blood pressure, heart rate, and oxygen saturation will be monitored as follows:
i. -5 minutes
ii. 0 (start of infusion)
iii. Post start of infusion: 5, 10, 15, 20, 25, 30, 35, and 40 minutes (end of infusion)
iv. Post end of infusion: Blood pressure will continue to be obtained until there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline diastolic blood pressure or diastolic blood pressure is below 85. Oxygen saturation will continue to be obtained until there are two measurements at least 15 minutes apart that are within normal limits (02 saturation of 94% or greater).
h. The **research assistant will remain outside the patients room during the infusion, and will record vital signs. A study physician will be available at all times**. After the subject is transferred back to their inpatient unit room, the blood pressure and heart rate will be obtained manually by the unit nursing staff.
i. Intervention for Hypertension: If the systolic blood pressure increases to ≥ 200 or diastolic blood pressure increases to ≥115 mmHg during the ketamine infusion, the infusion will be discontinued. The blood pressure will be monitored and if there is no decrease after 15 minutes, then we will initiate the following treatment interventions, consistent with our previous IRB-approved ketamine studies including IRB #6598:

1) One dose of sublingual nitroglycerine, 0.3 mg, will be administered.
2) If there is no response within 10 minutes, clonidine 0.1 mg po will be administered every 30 minutes (total maximum dose 0.6 mg clonidine) until the desired blood pressure is reached. Desired blood pressure is defined as within normal range or 10 mmHg of baseline diastolic reading.
3) If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER at New York Presbyterian Hospital. If they do not respond to the above treatment (1 and 2 above) then they will be transferred to the ER.

7. Post-infusion Neuroimaging:

a. PET imaging with [^{11}C]UCB-J, performed identically as described above, will be repeated as close to 24-48 hours following the 4th ketamine infusion as is possible with scheduling availability of the PET Center. If participants do not complete all four ketamine infusions for any reason (including adverse effects of ketamine, lack of clinical response and preference not to complete all sessions, etc), we may conduct repeat (post-ketamine) [^{11}C]UCB-J PET scan after fewer ketamine administrations.

8. Post-Infusion Treatment:

Pharmacologic treatment will proceed as follows at the conclusion of post-infusion PET and MRI acquisition:

Study participants will receive six months of open clinical treatment in the form of:

a) Continuation of inpatient treatment for as long as is clinically indicated, followed by

b) Outpatient psychiatrist visits for medication management with a psychiatrist in MIND to complete a total of 6 months of psychiatric care inclusive of the inpatient stay.

9. Exploratory research assessments of mood, suicidality, and side effects (per Fig. 1) Research assessments will continue for a three-week continuation phase post-infusion. Continuation phase clinical appointments will be weekly for four weeks, then decreasing to at least monthly, as clinically indicated, for the remainder of the six months.

Research assessments may be performed using phone or secure video (Webex or Zoom) and using Internet-based encrypted systems including Redcap or Citrix, managed by The NYSPI/Columbia School of Public Health Data Coordination Center (DCC).

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Withdrawal from Study: A subject will be withdrawn from the study if:

a. Subject requests to be removed for any reason.

b. The PI judges that it is medically unwise for the subject to continue in the study. For example, if the subject is unable to comply with the study procedures.

c. The subject is unable to tolerate the delay to treatment because of pronounced worsening of symptoms such as marked agitation or psychotic symptoms. Worsening of suicidal ideation will not automatically require discontinuation from research, as long as the team judges that the subject can be managed safely as an outpatient (e.g. they have no plan or intent), or they agree to inpatient treatment and the inpatient staff agrees that the patient may continue research participation. A CGI≥5 will trigger conversation with study PI regarding possible study discontinuation.

d. A rise in systolic blood pressure ≥ 200 mm Hg or diastolic blood pressure to ≥ 115 mm Hg during the infusion.

e. During infusion, if O2 saturation remains <94% with nasal canula oxygen, then subject will be withdrawn from research and treated clinically.

f. Other criteria for discontinuation will be appearance of psychosis, mania, severe

agitation, or other deterioration where the treating physician decides that research participation is unacceptable.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Sample	Collection Time Point	Total Collected per Participant
Blood	Baseline (through protocol 4815): 43ml Arterial blood sampling during PET scans, pre- and post-ketamine infusion: ≤100ml x 2 = ≤200 ml	Maximum blood drawn through both protocols collectively: ≤243ml

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Domain	Instrument	Time

Informed consent	IRB-approved form	30-45 min
Diagnosis	SCID-5	120 min
Demographics	Division Baseline Demographic form (BDEMO)	30 min
Clinical State	Hamilton Depression Rating Scale 24-Item (HDRS- 24)	10 min
	Beck Depression Inventory (BDI)	10 min
	Profile of Mood States (POMS)	10 min
	Clinical Global Impressions (CGI)	1 min
	Brief Psychiatric Rating Scale (BPRS) – 4 item positive symptom subscale	5 min
Medication	Past and Current Medications List	10 min
	Systematic Assessment for Treatment Emergent Events-General Inquiry (SAFTEE-GI)	10 min
	Clinician-Administered Dissociative States Scale (CADSS)	15 min
	Brief Psychiatric Rating Scale (BPRS) – Positive Symptoms Subscale Only	10 min
Biomarkers	Neuropsychological testing: Bushke, Stroop, Reaction Time, **Computerized Continuous Performance Test (CPT; 5 minutes), Computerized A, Not B Timed Reasoning Task (5 minutes), Computerized Go-No Go Task (5 minutes), WAIS-IV Coding Subtest (3 minutes)** @font-face {font-family:"Cambria Math"; panose-1:2 4 5 3 5 4 6 3 2 4; mso-font-charset:0; mso-generic-font-family:roman;	45 min

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Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
2

Drug #1

Name of the drug
Ketamine
Manufacturer and other information

Multiple generic manufacturers.

Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain

This is a clinical study involving a marketed drug and the study meets all of the following

conditions:

1. It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling; and

2. It is not intended to support a significant change in the advertising for the product; and

3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; and

4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 50 and 56 respectively]; and

5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

Drug #2

Name of the drug

[11C]UCB-J
Manufacturer and other information
[11C]UCB-J will be synthesized in the radioligand lab of the Columbia PET Center.
Approval Status
IND is approved
IND#
146646
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Miller, Jeffrey, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment

Patients on an antidepressant regimen at enrollment will continue their current antidepressant regimen; there will be no delay to that ongoing treatment for those participants. The delay to inpatient admission will not exceed 3 weeks; if a participant needs a longer delay between consent and beginning treatment for logistical reasons, it will be determined by the study clinician on a case-by-case basis based on need for delay, clinical stability, and ability to comply with the plan for monitoring. This period allows the time required for processing lab samples, completion of baseline research measures, and scheduling inpatient admission, the infusion procedures in the BSU, PET, and MRI procedures.

The delay to ketamine infusion will not exceed 4 weeks from the time of enrollment.

Thus, for participants not on an antidepressant regimen at the time of enrollment, the delay to the inpatient milieu, which has a therapeutic component, will not exceed 3 weeks, and the delay to pharmacologic intervention of ketamine will not exceed 4 weeks.

Maximum duration of delay to standard care or treatment of known efficacy

For participants not already taking an antidepressant, open pharmacologic antidepressant treatment will begin as soon as post-ketamine PET scan is completed; this will not exceed 7 weeks from the time of enrollment.

Treatment to be provided at the end of the study

Pharmacologic treatment will proceed as follows at the conclusion of post-infusion PET and MRI acquisition:

Study participants will receive six months of open clinical treatment in the form of:

a) Continuation of inpatient treatment for as long as is clinically indicated, followed by

b) Outpatient psychiatrist visits for medication management with a psychiatrist in MIND to complete a total of 6 months of psychiatric care inclusive of the inpatient stay.

Clinical Treatment Alternatives

Clinical treatment alternatives

Many treatments for MDD exist, such as numerous approved antidepressant medications, electroconvulsive therapy, and various evidence-based psychotherapies.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

1. PET Scan-Related Risks:

1A. Radiotracer

1A. Radiation exposure (PET)
For [^{11}C]UCB-J, the single scan injected dose limit is 740mBq or 20 mCi, yielding a cumulative protocol dose limit over two [^{11}C]UCB-J PET scans of 1480 mBq or 40 mCi. Single injection and annual exposures for all organs, as well as effective dose, are below limits set in 21CRF part 361.1. The risk estimate is based on the subjects in the study population who are most sensitive to radiation exposure.

Radiation Dosimetry			740MBq dose	740MBq dose x 2
	Organ	**µSv/MBq**	**mSv**	**mSv**

Active Blood-forming Organs	Red marrow	0.71	0.525	1.1
Gonads	Ovaries	0.64	0.48	0.96
3 highest organs	Liver	19.9	14.73	29.5
	Brain	17.4	12.88	25.8
	Kidneys	12.6	9.32	18.6
Whole Body		5.328	3.94	7.9
Effective Dose + 2 low dose CT attenuations per PET scan		3.32	2.55	5.09
Ref: J Nucl Med 2016; 57:777–784				

Transmission Scan NOTE: We plan to do the scans on the mCT scanner where the attenuation correction is done with a low-dose CT and therefore there will be a small amount of radiation due to the CT. In the event that the subject needs to leave the scanner while scanning (e.g. to use the bathroom) we will perform an additional low dose CT transmission scan (maximum total exposure from four CT scans ~0.176 mSv).

1B. Radiotracer physiological effects:

Consistent with previous work with [^{11}C]UCB-J (17), we will limit injected mass to 10 micrograms. The safety of [11C]UCB-J at similar injected masses has been demonstrated in PET studies published in the literature, including 10 healthy volunteers and 3 individuals with epilepsy in this study (17); five of whom received repeat [11C]UCB-J injections and scans the same day (20). Another study performed PET imaging with [^{11}C]UCB-J on 10 individuals with amnestic mild cognitive impairment and 11 individuals who were cognitively normal (21). The risk of an idiosyncratic reaction is acknowledged in the consent form. A physician will be **available** at the time of each injection of the radiotracer. Any adverse reaction to the radioactive drug (radiation related or not) will be reported to the NYPSI IRB and the JRSC.

1C. Placement of Intra-arterial catheter

Radial arterial catherization is needed for repeated arterial blood samples to construct tracer input curves. Complications resulting from such short-term catheterizations include bleeding, occlusion, clotting, or infection.

The following paragraph appears in the subject consent forms as per the IRB website, with one phrase added [shown here in italics] for more clarity for participants with lack of mathematical skills:

"The placement of a catheter in your artery may cause discomfort. There is a very small chance of complications from this catheter such as bleeding, bruising, infection or blood clot. There is an extremely low risk (0.09%, *or about 1 in a thousand*) of cutting off circulation to your hand which could result in a need for surgical repair or, in rare instances, could result in the loss of use of part of or all of the hand. These complications are rare and usually occur in medically ill patients who have catheters in their wrists for several days. In contrast, the catheter will remain in your arm for about four hours for this study. If you have a history of a bleeding disorder or are taking certain medications that affect blood clotting, you will not be asked to participate in this study."

The radial artery catheter is placed by an experienced physician.

1D. Intravenous catheter (PET, ketamine infusion)

There is a small risk of infection and bleeding associated with intravenous catheters, which are prevented by proper techniques. Placement of IVs will be by a physician, nurse, or technician trained and certified in aseptic technique for catheter placement to minimize this risk.

1E. Blood Drawing (PET, screening)

The risks associated with drawing blood are slight discomfort and occasional bruising. The total volume drawn through enrollment in this study and co-enrollment in our area's umbrella protocol, IRB #4815, is 243ml, which is less than the volume drawn during blood donation. We exclude individuals who are anemic with a Hemoglobin value <11 g/dL for females or <12 g/dL for males.

1F. Discomfort during scanning (PET and MRI)

It may be uncomfortable to lie motionless in the cameras (either PET or MRI) and it may cause some subjects to feel anxious. Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the scanner if requested. A benzodiazepine or antihistamine may be offered for the MRI scan for very anxious subjects.

1G. Pregnancy (PET, MRI, Ketamine)

Studies involving radiation are contraindicated during pregnancy because of possible risk to the fetus. Patients must agree at the time of consent to use an effective form of birth control and to inform the treating psychiatrist in the event of pregnancy while in the study. Women of child-bearing potential will have a serum pregnancy test administered as part of initial eligibility assessments, as well as urine pregnancy tests performed on the day of the PET and MRI scans prior to scanning, and **within a day prior to each ketamine infusion**. On the day of the PET scan, research staff will ask female participants whether they have had sex without birth control within two weeks of the PET scan. If they have, they will not be scanned that day. An additional urine pregnancy test will be administered one to two weeks after the second PET scan. The post-PET pregnancy test can be completed at NYSPI or by a take home urine pregnancy test (test kit to be provided by the study team) with email the subject informing the research team of the

results. Subjects will not be charged for the pregnancy test. In addition, nursing mothers will also be excluded from the study.

2. Side Effects of Intravenous Ketamine.
2A. Medical Risks related to Ketamine

Administration of sub-anesthetic doses of ketamine i.v., such as the 0.5 mg/kg dose to be used in this study, may induce a modest rise in blood pressure. We have administered sub-anesthetic doses of ketamine i.v. (0.5mg/kg over 40 minutes) in the setting of an IRB-approved MRI/MRS brain imaging protocol at this institution (IRB #5786, PI: J. Mann). The modest increases all peaked and largely resolved by 75 minutes, with vitals returning to near baseline.

In addition, ketamine may produce nausea and vomiting.

Procedures for minimizing risks related to Ketamine infusion:
Any medical risks from increased blood pressure will be minimized through the careful screening of potential subjects. Subjects will be excluded for baseline hypertension or any history of cardiovascular illness. A BLS-certified physician who has been trained in the infusion procedure will be present during the procedure. Procedures for hypertension that occurs during the infusion are described above under Study Procedures. Nausea and vomiting will be treated supportively and, if severe, with anti-emetic agents; if necessary, administration of ketamine will be discontinued. Subject will be informed that they should be fasting (12 hours no food, 4 hours no liquids) prior to the ketamine infusion.

2B. Psychiatric or Behavioral Risks Related to Ketamine

Ketamine is an FDA-approved dissociative anesthetic. Ketamine exposure at the sub-anesthetic dose to be used in this study can be associated with a moderate dissociative state, which is well tolerated in the majority of cases and is spontaneously reversible (22). There is extensive clinical experience with ketamine used at anesthetic doses, and no long-term detrimental effects of ketamine exposure have been reported. It is possible that ketamine administration will increase the risk of psychosis, even in normal subjects. Ketamine is a street drug of abuse. As such, it poses the risk that exposure during this study may predispose subjects to subsequent abuse of this drug. To minimize this risk, current drug or alcohol dependence or any history of ketamine abuse or dependence will be excluded. We will follow patients while they are receiving clinical treatment and review any evidence of abuse that may appear after the ketamine infusion. This dose of ketamine has been safely administered in similar settings to depressed patients with clinically significant suicidal ideation at least 23 times without any serious side effects (23, 24).
iv) Specific measures and precautions
The experiment will be carried out in the presence of at least one psychiatrist. In case of agitation, hyperarousal, or psychosis, the participant will be treated with benzodiazepine (lorazepam) or neuroleptics, as indicated.The risks of exposing subjects to a drug of abuse potential will be minimized by explaining this risk to prospective subjects, and by excluding from the study any subjects with documented or suspected current substance or alcohol dependence.

3. **MRI Scan**

The MRI scanner uses a large magnet to take pictures of the brain and is not associated with any known medical risks, except for persons who have a heart pacemaker, or have metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Patients will be asked to notify us if this is the case. There is also the risk of burns from medicinal patches during the MRI; therefore, subjects will be asked to remove any patches prior to the scanning session. Although there are no known risks associated with pregnancy, we will not scan someone who is known to be pregnant. Therefore, for women of childbearing potential, urine pregnancy testing will be conducted on the day of the MRI. Some people have reported sensations during the MRI scan, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your body. If the subject experiences sensations and feels uncomfortable, the MR technologist will stop the scan immediately. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's confined space. In our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped. Except for pacemakers and some types of metallic implants, we know of no health hazard from the MRI scan. The MRI scan is not painful, but having to lie still in the enclosed space of the scanning table is uncomfortable for some people.

Because this MRI scan is being performed for research purposes only, it may not show problems that would normally be found in a typical clinical MRI scan ordered by a doctor for a specific medical problem. The T1-weighted images acquired in this study, regardless of resolution of other image characteristics, do not, in general, yield adequate information for a clinical quality read. However, gross structural abnormalities such as the presence of mass effects or hydrocephalus will be examined and documented by an appropriately qualified radiologist. Upon request, results will be shared with research subjects or a physician designated by them.

4. Electrocardiogram

An electrocardiogram has no serious risks. On rare occasions a rash may develop where the electrodes are places which usually resolves without treatment.

5. Interviews

Interviews: Psychiatric interviews and neuropsychological testing can sometimes be boring or stressful, but some people find talking to a physician or psychologist helpful. The interviewers will all be experienced personnel. The research team may request permission to record the interview for teaching purposes with audiotape and/or videotape. In this event, a separate consent process will occur for this. Subjects may choose to postpone or stop the interview at any time.

6. EEG/ERP Tests

The procedures for measuring EEG are noninvasive and standard for clinical research in this area and represent no risk to subjects. Subjects may experience some discomfort when applying the electrode cap but this passes quickly. In our prior work, subjects have experienced little difficulty

doing resting EEG or LDAEP tasks. Testing procedures are designed to maximize the mental and physical comfort of the participants and represent no risk to them.

7. COVID-19

There is a risk of being infected with COVID-19 while traveling to and from the medical center. In order to minimize the risk of travel we will instruct all subjects in the importance of social distancing and wearing a mask at all times during travel to and from NYSPI as well in NYSPI. On the day of the PET and MRI scans we will offer to pay for an Uber ride for subjects living in the extended New York metropolitan area.

Describe procedures for minimizing risks

Procedures for minimizing risks are integrated into the risks section above.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

Personal information will be kept confidential and will not be released without the subject's written permission except as described in this section or as required by law. The subject's name or other identifying information will not be made known if the results of this study are published for scientific purposes. Clinical records, including the subject's name and other personal identifying information, and research data will be kept in secure storage at the New York State Psychiatric Institute. Information in paper format will be kept in locked files. Electronic data, including MRI images, will be protected by a firewall (programming that makes it virtually impossible to access the data from outside the New York State Psychiatric Institute) and by restricting access within the New York State Psychiatric Institute through use of a password known only to authorized personnel. If information is transmitted electronically, it will be encrypted so that identifying information remains confidential.

The subject's information will only be available to study research staff and other authorized individuals, including those at the New York State Psychiatric Institute, New York State and federal regulatory agencies such as the Food and Drug Administration who may review records as part of routine audits. There are also legal advocacy organizations that have authority under New York State law to have access to otherwise confidential subject records, although they cannot disclose this information without the subject's consent.

The subject's MRI will be interpreted and the results will be shared with the subject or physician who the subject may designate. The MRI report will be maintained as part of the clinical database at the Columbia Radiology MRI Center at the Neurological Institute along with the subject's name

and will be accessible to clinicians at the New York State Psychiatric Institute. The subject's psychiatric diagnosis will not be a part of the report.

Data will be de-identified prior to publication in the scientific literature and presentation at scientific meetings,

Data collected in this research study, including MRI and PET scans, measurements from blood samples drawn during the PET scan, and questionnaire answers, may be used in future studies, and may be shared with other investigators after being de-identified, including in scientific data banks. There is a potential risk of loss of confidentiality from such data sharing, but this is extremely low as only de-identified data from this study may be shared.

While we perform analyses of the blood samples that are drawn during the PET scan in this protocol, no biospecimens are banked/stored through this research study, and as such, no actual biospecimens from this research study will be shared with other investigators (though the results of blood assays may be shared as above).

All screening and consenting procedures will be done remotely over a HIPAA-compliant videoconferencing software (Webex or Zoom) or telephone. We will document consent electronically using Redcap. The consent discussion process will include discussion of the HIPAA-compliant, encrypted platforms to be used. We will discuss any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi, and attempt to address these concerns to the best of our ability.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects

This study was not designed for the direct benefit of participants.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

Participants who complete all neuroimaging assessments (baseline PET, baseline MRI, and post-treatment PET) will be compensated $600. Individuals who complete a subset of these procedures will be compensated based on the components that they complete ($150 for each PET scan and $100 for each MRI).

Payment procedures are initiated upon subjects' completion of the study. Payment is in the form of a check, usually received in the mail about 4-6 weeks after completion of the study procedures.

References

References

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Statistical Analysis Plan

This is a pilot study examining the relationship between synaptic density quantified by PET imaging with [11C]UCB-J and clinical outcomes following treatment with ketamine infusions for depression.

Primary aims will be assessed using linear mixed effects models. All tests will be performed using two-sided alternatives with alpha=0.05. For all analyses we will examine standard diagnostic plots to identify evidence of lack of model fit, presence of outliers or overly influential points, etc., and take appropriate remedies as indicated (e.g., review source data of outliers, transform data, etc.).

As this is a pilot study, additional exploratory analyses will be conducted for hypothesis generating purposes.