New York State Psychiatric Institute

Institutional Review Board

March 21, 2017

To: Dr. Daniel Javitt

From: Dr. Edward Nunes, Co-Chairman, IRB
Dr. Laurence Greenhill, Co-Chairman, IRB

Subject: **APPROVAL NOTICE**: **CONTINUATION APPROVAL**
EXPEDITED PER 45CFR46.110(b)(1)(f)(8)(c)

Your protocol **#6925** entitled: **BIOMARKER ASSESSMENT OF GLUTAMATERGIC TARGET ENGAGEMENT** ACAR/PSF version date 3/13/17 and consent forms (version) have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **APRIL 7, 2017 TO APRIL 6, 2018.**

Consent requirements:

X Not applicable: (RECRUITMENT COMPLETED. DATA BEING ANALYZED)

☐ 45CFR46.116(d) waiver or alteration of consent for the telephone screen.

☐ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

CC: RFMH (HHSN27100003)
CUMC-IRB (no number assigned)
CU Grants & Contracts

EN/LG/ls

Signed copy on file at IRB

Protocol Title:
Biomarker Assessment of Glutamatergic Target Engagement

Version Date:
03/21/2017

Protocol Number:
6925

First Approval:
05/05/2014

Clinic:
Leiber Research Clinic

Expiration Date:
04/06/2017

Contact Principal Investigator:
Daniel Javitt, MD, PHD
Email: dcj2113@columbia.edu
Telephone: 6467745404

Co-Investigator(s):
Lawrence Kegeles, MD
Jeffrey Lieberman, MD
Alayar Kangarlu, PHD
Ragy Girgis, MD
Jacob Ballon, MD
Joshua Kantrowitz, MD
Pejman Sehatpour, PHD

Research Chief:
Daniel Javitt, MD, PHD

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

Division & Personnel

Division

What Division/Department does the PI belong to?
Experimental Therapeutics
Within the division/department, what Center or group are you affiliated with, if any?
Experimental Therapeutics

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.
This study is a three site study being performed as part of the FAST network (overall PI: Lieberman). The other two sites are UC-Davis (PI: Cameron Carter) and Yale Univ. (PI: John Krystal). However, each site will perform its own study and RFMH/NYSPI/Columbia will be the coordinating site. No human subjects work will be shared between sites. No confidential health information will be shared between sites.

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Study was completed November 2015. Currently exploratory analysis is ongoing with a draft manuscript in progress. Results from this study informed the design of IRB study #7285 (ongoing).

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes

Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
12/31/2016

Overall Progress

Approved sample size
300
Total number of participants enrolled to date
138
Number of participants who have completed the study to date
31
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
Because of very strict inclusion/exclusion criteria, which were in place to maximize the safety of the subjects, we had to screen fail the vast majority of participants enrolled in the study.
Comments / additional information
Study completed November 2015. Only data analysis ongoing

Sample Demographics

Specify population
Healthy Control Subjects
Total number of participants enrolled from this population to date
138
Gender, Racial and Ethnic Breakdown

Male: 91
Female: 47

Caucasian: 26
Hispanic: 25
African-American: 74
Asian: 9
Other: 4

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?

No
Did participants decide to discontinue study involvement?
No

Procedures

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

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ MRI
✓ Biological Challenge Procedure
✓ Administration of Substance of Abuse

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50

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
1

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
Federal
Institute/Agency

NIH/NIMH
Grant Name
mGluR2/3 Study/Trial HHSN27120120000I FAST-PS
Grant Number
HHSN27100003
Select one of the following
Multicenter(NYSPI is the lead site)
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia, Yale, UC Davis. As above, Yale and UC Davis will be performing the same study. However, the studies will run independently and no confidential information will be shared between the sites. The anonymized data will be pooled for analysis.

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
Yes
✓ Hospital, clinics and other healthcare facilities

Hospitals,clinics and other healthcare facilities

Select from the list
or type in location(s)..
We will have the option of admitting subjects after receiving ketamine to the Irving Institute's inpatient unit.

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Prefrontal glutamatergic hyperactivity is hypothesized to underlie persistent positive symptoms of schizophrenia and prefrontal dysfunction as manifest in deficits in executive function and working memory. mGluR 2/3 receptors regulate presynaptic glutamate release in brain, leading to the hypothesis that they should exert a pro-therapeutic effect. Contrary to this expectation, however, the mGluR 2/3 agonist Pomaglumetad (LY2140023) was entered into a phase III clinical trial program and, despite adequate statistical power, was found to be without therapeutic effect. It is thought that the lack of target engagement

of this agent may have been responsible for this negative finding, though this is not known as no measures of target engagement were used in this trial.

The purpose of this study is to assess the relative feasibility of 2 potential functional measures of target engagement (Glx MRS, BOLD fMRI) systematically assess mGluR 2/3 in drug development for psychotic spectrum disorders. We will recruit 18 subjects, each of whom will be randomzied to ketamine or placebo in a 2:1 ratio and receive two drug challenges separated by at least two weeks. Ketamine challenge is used to induce a "glutamate surge" within prefrontal brain regions that can be detected using neurochemical and functional imaging techniques. Each subject will receive MRS and BOLD fMRI during each challenge day. The goal of the pilot study is to assess the feasibility of both the proposed ketamine challenge paradigm and of the proposed imaging-based biomarkers. Specific indices to be used in assessing feasibility will include effect size, cross-site and cross-subject reliability, safety, and subject tolerability as similar studies will be performed independently at Yale and UC-Davis. Second, this information will be used to select and refine final study parameters for a subsequent full proof-of-clinical mechanism (POCM) study investigating the effect of Pomaglumetad on ketamine-induced MRS and fMRI effects.

This protocol describes only the pilot study. The second stage, POCM full study will be described in a separate protocol.

Background, Significance and Rationale

Background, Significance and Rationale

Activation of metabotropic glutamate receptors (mGluRs) triggers second messenger systems and affects neuronal metabolism. Group II metabotropic receptors (mGluR 2 and 3) regulate presynaptic glutamate release and postsynaptic sensitivity by limiting glutamate release during conditions of glutamate spillover from the synaptic cleft (Kantrowitz and Javitt, 2009). The potential use of mGluR 2/3 agonists in the treatment of schizophrenia is based upon the hypothesis that increased cortical glutamate levels, as detected by MRS, may be pathophysiological (Homayoun and Moghaddam 2007), and that compounds such as mGluR 2/3 agonists may be capable of reducing abnormal glutamate levels and thus be therapeutically beneficial. mGlu2/3 receptors are primarily located in the prefrontal cortex, suggesting a particular impact on cognition and positive symptoms as reviewed in (Herman et al., 2012).

Evidence of abnormally elevated cortical glutamatergic compounds in schizophrenia has been consistently seen in MRS studies of unmedicated patients (Bartha et al, 1997; Theberge et al., 2002 and 2007; de la Fuente Sandoval et al., 2011; Kegeles et al., 2012). These studies reported elevations in glutamate, glutamine, or their combination, Glx. One study reported a positive correlation between Glx levels and positive symptoms (Kegeles et al., 2012).

At present, positive symptoms in schizophrenia are treated using typical/atypical antipsychotics, which function primarily by blocking dopamine D2 receptors. While effective, such compounds are poorly tolerated and associated with both motor/metabolic side effects and high rates of discontinuation

(Lieberman et al., 2005; Kahn et al., 2008). mGluR 2/3 agonists might be uniquely effective as non-dopamine antipsychotics and better tolerated with fewer side effects, as observed in the initial Lilly phase II study (Patil et al., 2007). However, initial positive results were not replicated in subsequent studies (Kinon et al., 2011), leading to a recent decision by the company to discontinue clinical development. Nevertheless it remains unclear whether these trials failed due to failure of the target itself vs. failure of the compound to adequately engage the target at the doses used. Our goal in this trial is to assess target engagement by an mGluR 2/3 agent when administered at doses below, within, and above the range studied in these clinical trials.

To do so we will administer the mGluR 2/3 agent (pomaglumetad) to healthy subjects after ketamine challenge and use MRI-based imaging to measure target engagement by pomaglumated. However, before we perform this proof of clinical mechanisms study with pomaglumetad, we will assess the feasibility of Glx MRS **and** BOLD fMRI to measure ketamine induced changes in glutamatergic indices in a pilot study of healthy subjects.

This study is part of the FAST initiative sponsored by the NIMH. Three sites (RFMH/Columbia, Yale, UC-Davis) will be independently performing these studies. The current protocol only applies to the pilot study (N=18) which does not include pomaglumetad administrations.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Specific Aim 1: Compare changes in Glx in response to infusion of ketamine vs placebo, as measured by MRS. We hypothesize that ketamine will lead to statistically significant increases in Glx in anterior cingulate cortex as compared to placebo.

Specific Aim 2: Compare changes in basal fMRI BOLD signal ("pharmcoBOLD") in response to infusion of ketamine vs placebo. We hypothesize that ketamine will lead to statistically significant increases in BOLD signal in dorsolateral prefrontal cortex and hippocampus compared to placebo.

Specific Aim 3: Compare changes in task-related fMRI BOLD response ("task related BOLD") in response to infusion of ketamine vs. placebo. We hypothesized that ketamine will significantly reduce task-related BOLD activation in in dorsolateral prefrontal cortex and hippocampus.

Specific Aim 4: Determine the feasibility and compare the relative strengths and weaknesses of the proposed MRS and fMRI biomarkers.

Description of Subject Population

Sample #1

Specify subject population
Healthy Control Subjects
Number of completers required to accomplish study aims
48
Projected number of subjects who will be enrolled to obtain required number of completers
300
Age range of subject population
18-55

Gender, Racial and Ethnic Breakdown
We aim to include subjects of both genders in equal numbers. The ethnic composition of the group will reflect the ethnic composition of subjects recently recruited for imaging studies by our investigators (42% Caucasian, 22% Hispanic, 24% African-American, 12% Asian).
Description of subject population
As above.

Recruitment Procedures

Describe settings where recruitment will occur
Healthy volunteers will be recruited from advertisements in local newspapers and posted ads in campus settings and throughout NYSPI. Advertisement on research websites, or on sites such as Craig's List, will also be used.

"Umbrella" approaches, such as listing on clinicaltrials.gov, may also be used. All recruitment materials will be approved by the local IRB prior to distribution.

How and by whom will subjects be approached and/or recruited?
Subjects who respond to the advertisements are contacted by phone by study personnel. Potential subjects are explained the nature of the study and undergo a brief screening on the phone. If they are interested, they are invited to come in for the screening process.
How will the study be advertised/publicized?
Healthy volunteers will be recruited from advertisements in local newspapers and posted ads in campus settings and throughout NYSPI. Advertisement on research websites, or on sites such as Craig's List, will also be used.

"Umbrella" approaches, such as listing on clinicaltrials.gov, may also be used. All recruitment materials will be approved by the local IRB prior to distribution.

Do you have ads/recruitment material requiring review at this time?
No

Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02134951

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Healthy control subjects may also be recruited from IRB # 6731R (Abi-Dargham), #6654R (Girgis), or **#7114 (Corcoran)**.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Healthy Control Subjects
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria	Assessment
1. Age Between 18 and 55	History
2. Negative Urine Toxicology	Urine Toxicology
3. No present or past psychiatric conditions (including substance abuse or dependence, with the exception of nicotine dependence)	SCID and/or DIGS
4. No family history of schizophrenia in a first-degree relative.	History

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

Exclusion Criteria	Assessment
1. Any current DSM IV Axis I disorder and/or past substance abuse or dependence (nicotine dependence is allowed)	SCID and/or DIGS
2. Any current use of amphetamines, opiates, cocaine, sedative-hypnotics, or cannabis	Urine Toxicology, History
3. Current (i.e., within the last 3 months) treatment with any psychotropic medications	History
4. Pregnancy, lactation, or lack of use of effective birth control	History, Serum pregnancy test at screening and urine

	pregnancy test on MR scan day
5. Presence or positive history of significant medical or neurological illness (including any history of seizure or mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the CNS, or history of significant head injury), including high blood pressure (SBP > 140, DBP > 90), low blood pressure (SBP < 100, DBP < 60), orthostatic BP change > 20% (1/3 SBP + 2/3 DBP) or cardiac illness or resting heart rate >100 or <50	History, EKG, laboratories (blood and urine)
6. History of significant violent behavior including any history of using a gun, knife, or other weapon with intent to harm someone, as well as a more than one physical fight without a weapon after the age of 18 years old (not including fights that happen during sports competition).	History
7. **History of recreational ketamine use, recreational PCP use, or an adverse reaction to ketamine. Subjects who have participated prior research ketamine studies will be eligible providing they have participated in no more than 5 previous research ketamine infusions. Subjects can have infusions not more frequently than biweekly, and not more than 1/month on average, therefore subjects entering the study will need to wait 1 month if they had a single infusion and 6 weeks if they have had two closely spaced infusions.**	History
8. Contraindication to MRI scanning, including metal implants or claustrophobia. Metal implants, pacemaker, other metal (e.g. shrapnel or surgical prostheses) or paramagnetic objects contained within the body which may present a risk to the subject or interfere with the MR scan, as determined in consultation with a neuroradiologist and according to the	History

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,	
8. Color Blindness	**History**

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
Yes
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
As below.
Describe Study Consent Procedures

The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential subjects. The process begins with the subject initiating contact via telephone. The research staff provide a brief description of the study following which the subject is screened by a member of the research team. Thereafter, potentially eligible candidates are scheduled for an in-person visit.

Subjects will be informed of all potential risks of participation. Subjects will be required to read the informed consent form, and the investigator additionally describes the risks and discomforts. To ensure that the study subject understands the study, the subject will be asked questions about the study procedures and the risks associated with participation. If any concern arises that the study subject did not fully understand the study, the PI may decide that the subject is not suitable for participation. This process generally takes about 1 hour. If the subject is still interested, after all questions have been answered, the PI will ask the subject to sign the informed consent form. Any subject who appears incapable of providing informed

consent will be excluded. Subjects will be informed that they can decline to participate in the study without penalty, and can withdraw from the study at any time prior to analysis of their data. Following the resolution of any questions, the subject will be asked to sign the consent form, if he/she agrees to participate.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
Yes
Is breach of confidentiality the main study risk?
Yes
Describe the study component(s) for which waiver of documentation is requested

We request a waiver of documentation of consent only for the phone screen:

We are doing a study that involves receiving ketamine twice and an MRI. In order to be eligible, you need to not have a psychiatric illness or take any psychiatric medications, be medically healthy, not abuse drugs or alcohol or be currently depressed. With a yes or no answer, do you think you would a good fit for this study?

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Girgis, Ragy, MD
Javitt, Daniel, MD
Kantrowitz, Joshua, MD
Kegeles, Lawrence, MD
Lieberman, Jeffrey, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Screening

After providing informed consent, subjects will undergo full medical screening (i.e., medical history, physical examination, laboratories for basic chemistries, blood counts, liver function tests, urinalysis, urine toxicology, serum pregnancy test for women, and thyroid tests, electrocardiogram [EKG]) and psychiatric

screening (i.e., Structured Clinical Interview for DSM IV Axis I Disorders (SCID) (First et al., 1996) or Diagnostic Interview for Genetic Studies (DIGS) Nurnberger et al., 1994) to confirm eligibility. Screening will occur over an up to 21-day screening period. Screening procedures covered in other protocols at NYSPI will not be repeated unless necessary.

Experimental Procedures (Both Day 1 and Day 14 except where noted)

After screening, each eligible subject will be randomized in a 2:1 ratio to ketamine or placebo (normal saline) and receive 2 study drug infusions separated by 2 weeks. During each study drug infusion they will receive MRS and BOLD fMRI. Subjects randomized to ketamine will get ketamine on both scan days, subjects randomized to placebo will get placebo on both study days. This study will be performed double blind.

Pregnancy test (urine) on scan day
Female subjects undergo a urine pregnancy test on each scan day to assure that pregnancy has not occurred between the time of the screening and the study.

Subjects will also receive urine toxicology on every scan day.

Ketamine/placebo infusion

An intravenous infusion of saline solution with ketamine at a rate and dose of 0.23mg/kg bolus over 1 minute followed by 0.58 mg/kg/hr over 30 minutes then 0.29 mg/kg/hr over 64 minutes (Ketalar; Parke Davis, Morris Plains, NJ) will be given (or normal saline for people in the placebo group). Similar doses have been safely administered by collaborators of ours on this project more than three dozen times without any serious side effects (D'Souza et al., 2012a, D'Souza et al., 2012b). We have experience infusing similar doses (0.77 mg/kg and 1.8 mg/kg) at this institution under IRB protocols #1350 and #1474 (Kegeles et al., 2000). An ACLS certified RN or MD will be present during the ketamine infusion. To avoid multiple needle sticks for drawing the blood samples for ketamine and norketamine levels, a second venous line will be placed.

Vital signs monitoring

EKG and pulseox will be constantly monitored prior to, during, and after the ketamine infusion until the end of the MRI scan. Blood pressure will be monitored and recorded at 5-minute intervals at baseline and throughout the ketamine infusion, and at 10 minute intervals following the end of infusion until the end of the scan (at least 120 minutes post initiation of ketamine infusion).

MR Acquisition

All subjects will receive MR scanning before, during and immediately following the administration of ketamine/placebo. MR scans will be performed at the NYSPI MRI facility using the 3.0 Tesla GE scanner. Scans will include quantitative MRI structural imaging for optimal segmentation of brain tissue into gray and white matter and cerebrospinal fluid. All scans will include MR spectroscopy acquisitions with GABA and glutamate-glutamine spectroscopic editing. fMRI will be performed using CNTRICS tasks to assess the

effects of ketamine on circuitry associated with encoding and retrieval. This sequence of MR scans will last no more than 180 minutes. We will obtain both T1- and T2-weighted images.

fMRI Task

Task design is based on a previous validation study (Ragland et al., 2012), using the RISE task by the CNTRACS consortium, which demonstrated the sensitivity of the task to group differences in relational memory and good test-re-test reliability of the task, adapted for the imaging environment. During encoding, participants are presented with 54 pairs of common visual objects. Objects are presented for 4 seconds each with a "jittered" variable inter-trial interval of 1-10 seconds (4 seconds average). Stimuli are presented during one of two conditions: 1) During item encoding, participants are asked to use a two-button response pad to answer "yes" or "no" to indicate whether either of the objects presented are living. During relational encoding, participants are asked to answer "yes" or "no" to indicate whether either of the objects could fit inside the other. Participants are encouraged to respond as quickly and accurately as possible, and guess if unsure. Encoding conditions are randomly alternated between 6 blocks of 9 trials each, and an instruction screen announces the encoding condition ("Living" or "Together") at the beginning of each block.

Following encoding, participants are presented with an item recognition task in which they are shown 108 single objects from the pairs of objects studied during the encoding task, together with 54 new objects (i.e., foils) not previously presented. Objects are presented for 3 seconds each with a variable inter-trial interval of 0-10 seconds (3 seconds average). The recognition task is divided into 2 runs of 81 trials each. For each object, participants are required to indicate whether the object is "old" or "new" using a two-button response pad. Participants are encouraged to respond as quickly and accurately as possible, and guess if unsure.

Item recognition is followed by an associative recognition task in which participants are presented with 27 "intact" pairs from the relational encoding condition (i.e., both objects were presented together during encoding) intermixed with 27 "re-arranged" pairs from the relational encoding condition (i.e., objects were presented during encoding but were members of different pairs). Objects are presented for 3 seconds each with a variable inter-trial interval of 0-10 seconds (3 seconds average). During associative recognition runs, participants are asked to use a two-button response pad to respond "yes" if the pairs are intact, and "no" if they were re-arranged. They are again encouraged to respond as quickly and accurately as possible, and guess if unsure.

Behavioral ratings, Plasma ketamine/norketamine levels, and post-infusion observation.

Subjects will be rated with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Profile of Mood States (POMS) (McNair et al., 1981), and Clinician Administered Dissociative Symptom Scale (CADSS) (Krystal et al., 1994)instruments at baseline and after the ketamine infusion and scanning period. Ratings on the Psychotomimetic States Inventory (PSI) will also be obtained (DeSimoni et al., 2013).

Venous blood samples (5 mL each) will be drawn at up to three times during study drug infusion for assay at the Analytical Psychopharmacology laboratory.

All subjects will be asked to stay for at least 2 hours post-infusion. In this time they will be evaluated for a potential admission to the Irving Center.

After the imaging day procedures are completed, subjects will be evaluated by a study physician before discharge. Subjects will be given the contact information for a study physician in the case that a medical issue arises after discharge.

Irving Center admission

Following each ketamine infusion, subjects will be evaluated for admission to the Irving Institute for Clinical and Translational Research Clinical Research Center for an overnight stay following the session. If clinical evaluation determines that effects of the study drug infusion have resolved to the point that subjects are safe to return home, they will be discharged from the study without admission to HP10. These evaluation criteria will consist of absence of significant deviations from baseline in vital signs, gait, mental status exam, and BPRS and CADSS scales as determined by a study physician. Subjects will be medically and psychiatrically stable before transfer to the Irving Center unit. Any subject who is not stable after the study procedures as determined by the study physician will be admitted instead to the Emergency Department at New York Presbyterian Hospital. Subjects will be cleared by physician for discharge from the Irving Center the morning after ketamine administration.

Additional Safety Measures

The SAFTEE (Levine and Schooler, 1986) will be used to assess general side effects and will be performed after study procedures on Days 1 and 14 (scan days), as will vital signs assessment. If necessary, subjects will be asked to return one week after completion of the active phase of the study to follow up on any abnormalities in EKG, physical examination, or laboratories. Vital signs, including orthostatic blood pressure monitoring, will also occur on the study procedure days. Study staff will also call subjects one day, one week, and one month after the second study drug infusion in order to follow up on the subjects' clinical status.

Additional Pilot Subject

The first subject (n=1) of this study will undergo all of these procedures as specified above except will only undergo one scan day (and one study drug infusion). The purpose of this subject is to pilot the procedures. A separate CF will be produced for this subject.

Stand By

We will give all subjects the option of being a standby subject. Standby subjects will be asked to come in on a day when a brain scan is scheduled for another participant. If for some reason the original participant does not complete the imaging procedures, the standby will be asked to participate in the imaging procedures in place of that person. If the original participant does complete the imaging procedures, they

standby will be sent home. We expect that standbys will have to wait between 1-3 hours as a standby participant. Subjects can choose to be a standby subject by checking one of the boxes found at the end of the consent form. We may ask standbys to be standby subjects multiple times. In addition, we may schedule more than one standby for a given day.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

- Clinically significant adverse events, which would be inconsistent with continuation in the study

- Clinical judgment of the investigator or at request of subject, sponsor, or regulatory authority

- Withdrawal of consent and/or patient decision

- Pregnancy or loss to follow up

- Any evidence of suicidality/homicidality **(as assessed by the by a clinical interview by the study psychiatrist on every visit)**.

- Treatment with a **new** medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;

-Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures;

-Systolic BP increases to > 180 mm Hg and remains > 180 mm Hg for more than 2 minutes, or diastolic BP increases to > 110 mm Hg and remains > 110 mm Hg for more than 2 minutes.

-They experience an adverse reaction to ketamine including emergence of psychosis.

Blood and other Biological Samples

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

Screen	Study Days	Follow Up	Total (cc)	Total oz (tbsp.)
15 cc	15cc * 2 = 30cc	15cc	60	2.03 (4)

Assessment Instruments

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

Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962): measures overall psychiatric symptomatology, 15 minutes

Clinician Administered Dissociative Symptom Scale (CADSS) (Krystal et al., 1994): 5 minutes, measures dissociative symptoms related to ketamine infusions

Psychotomimetic States Inventory (PSI) (DeSimoni et al., 2013)- measures psychotomimetic symptoms related to ketamine infusion 15 min

Profile of Mood States (POMS) (McNair et al., 1981)-measure mood symptoms related to ketamine infusions, 10 minutes

SCID (First et al., 1996)-diagnostic interview, 1 hour

DIGS (Nurnberger et al., 1994)-diagnostic interview, 1-1.5 hours

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
n/a. Subjects are healthy volunteers, not in treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Potential Risks and Protections Against Risks

Risks associated with the study are related to: a) Ketamine administration; b) MR scans; c) venous blood sampling; d) intravenous catheter; e) interviews and neuropsychological assessments.

Ketamine Administration

Medical Risks: Studies will be performed in the presence of an ACLS-certified RN or MD, and subjects will be under constant monitoring by EKG and pulse oximeter, as well as by frequent blood pressure measurements. Subjects will as usual in the MRI scanner have constant communication access to staff through a sound pipe as well as through an emergency "squeeze bulb" communication system.

Administration of subanesthetic ketamine i.v. induces a modest rise in blood pressure and pulse. We have administered subanesthetic doses of intravenous ketamine in the setting of numerous published brain imaging studies with IRB approval. A range of doses have been studied by the investigators of this protocol. Here we report on data published by Dr. Lawrence Kegeles, a co-investigator of this study. In the first study, ketamine was administered at 0.2 mg/kg intravenous bolus plus 0.4 mg/kg/hr for 4 hours, for a total dose of 1.8 mg/kg (n=8 healthy volunteers) (Kegeles et al., 2000). In the second study, ketamine was given as an intravenous bolus (30 sec) at a dose of 0.12 mg/kg, followed by a constant infusion over the next hour of another 0.65 mg/kg, for a total dose of 0.77 mg/kg (n= 10 healthy volunteers) (Kegeles et al., 2002). In the first study, the resulting effects on vital signs for a group of 6 healthy volunteers are presented as a function of time in th**e table** below for the first 50 minutes post-injection. These modest increases all peaked and largely resolved by 50 minutes, with vitals returning to near baseline, at which time subjects were mobilized for the first SPECT scan. Administration of subanesthetic doses of ketamine can induce nausea and vomiting. Of the six subjects whose vital sign data are presented below, one withdrew because of nausea and vomiting, and another suffered from these symptoms. In a more recent, lower-dose ketamine administration protocol identical to the one proposed in this application, all subjects have been free of nausea and vomiting.

Table. Effects of ketamine on systolic and diastolic blood pressure in a group of normal subjects (n=6).

Time (min)	Systolic Blood Pressure after Ketamine (mm Hg)	Diastolic Blood Pressure after Ketamine (mm Hg)	Pulse after Ketamine (min^{-1})
-2.5	115.5	70.5	71.5
0.0	146.0	81.8	99.8
5.0	150.8	87.8	92.2
10.0	150.6	94.6	89.6
15.0	142.0	81.3	82.5
20.0	146.8	80.8	73.8
25.0	142.0	67.0	86.0
30.0	153.3	85.0	88.3
40.0	133.0	77.3	80.3
50.0	125.0	72.7	78.3

These adverse effects will be minimized by excluding participants with a history of cardiovascular disease, by conducting a baseline physical examination to evaluate possible hypertension, by obtaining a baseline EKG, and by monitoring EKG, pulse, oxygenation, and blood pressure during ketamine administration.

Ketamine has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus. However, given the risk of ketamine inducing psychiatric symptoms, the risk/benefit ratio is not favorable for this population; hence, pregnant females or nursing females are excluded from the study. All female subjects will demonstrate a negative human chorionic gonadotrophin (HCG) blood test prior to study entry.

Psychiatric or Behavioral Risks:

Ketamine is an FDA-approved dissociative anesthetic. Ketamine exposure at the subanesthetic 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 spontaneously reversible (Krystal et al., 1994). 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, sometimes called 'special k.' As such; it poses the risk that exposure during this study may predispose subjects to subsequent abuse of this drug.

Initial risk will be minimized by medical and psychiatric screening during the screening/consent procedure as described above. The experiment will be carried out in the presence of at least one psychiatrist and an ACLS-certified RN or MD. Medical risk will be monitored and minimized by use of continual EKG, heart rate and pulse oximetry monitoring as well as frequent blood pressure readings. The risks of exposing healthy subjects to a drug of abuse potential will be minimized by explaining these risks to prospective subjects, and by excluding from the study any subjects with documented or suspected prior substance or alcohol abuse history. In addition, all subjects will, if not cleared for discharge by a study physician the afternoon after the study, be admitted to the research unit at the respective site if needed for observation and supportive treatment. If admitted, subjects will undergo assessment for clearance for discharge, at the earliest the morning following the study. Subjects will be followed up by telephone by research staff one day, one week and one months later, for any possible adverse outcomes related to administration of ketamine. Finally, the Data and Safety Monitoring Plan and Board will have as a central focus the risks and protections against risk of administration of ketamine (see below).

Additionally, our group has prior experience with multiple i.v. infusions of subanesthetic doses of ketamine and demonstrated its safety, as well as its lack of additional effect on neurochemical response (Kegeles et al., 2002). Therefore, we do not expect additional safety issues with two doses compared to one dose. To maximize the safety of two doses of ketamine, we are separating the doses by 2 weeks.

MRI scanning

It may be uncomfortable to lie motionless in the scanner (MRI) and it may cause some subjects to feel anxious.
While there have been no reports of any long-term effects caused by magnets of the same or even higher strength, the long-term effects of being placed in a magnet of this strength (3 Tesla)

are unknown. 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. Subjects 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. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. Therefore, for women of childbearing years, pregnancy testing will be conducted 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. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner’s small space. Despite these sensations, in our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped.

Venous Blood Sampling

Blood sampling in the amount of 15 mL or 1 tablespoon for screening laboratory tests and follow up laboroatory tests and an additional 30 mL for ketamine/norketamine levels is at a minimal level of risk, which includes slight pain, the possibility of bruising, and the possibility of feeling faint. Subjects will be advised of these risks.

Intravenous Catheter

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 or nurse trained and certified in aseptic technique for catheter placement to minimize this risk.

Interviews and Neuropsychological Assessments

Interviews and neuropsychological assessments are associated with minimal risk. Some participants may find the interviews and assessments tiring or distressing.

Describe procedures for minimizing risks
1a) Medical risks.
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. In addition, an ACLS certified RN or MD will be present during the procedure. During the ketamine infusion, vital signs (blood pressure and heart rate) will be monitored as
follows:
• -5 minutes
• 0 (start of infusion)
• Post start of infusion: every five minutes until the end of infusion
• Post end of infusion: Every 10 minutes for remaining duration of the scan.

After subjects are transferred back to the examination room, blood pressure will be obtained until there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline diastolic blood pressure. After the subject is transferred back to the examination room, the blood pressure and heart rate will be obtained manually by the research assistant or nurse. If the systolic blood pressure increases to > 180 or diastolic blood pressure increases to > 110 mm Hg for more than 2 minutes during the ketamine infusion, the infusion will be permanently discontinued and the study terminated. The blood pressure will be monitored and if there is no decrease after 5 minutes, then:
a. One dose of sublingual nitroglycerine, 0.3 mg, will be administered.
b. 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 10 mm Hg of baseline diastolic reading. If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER.
By following this protocol for hypertension management, the medical risks involved in participation in this study will be minimized.
Females in the study who are capable of becoming pregnant must either be abstaining from sexual intercourse for the duration of the study or be using a medically acceptable form of contraception. Reliable methods of preventing pregnancy are hormonal contraceptives (the pill), barrier methods (condoms), intra-uterine devices, and tubal ligation.

1b) Psychiatric or behavioral risks.
The experiment will be carried out in the presence of at least one psychiatrist. Severe agitation or hyperarousal will be treated with intravenous diazepam or neuroleptics, as indicated, and the study terminated. The risks of exposing healthy 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 prior substance or alcohol history of dependence or abuse as outlined in the inclusion/exclusion criteria. Subjects may be admitted to the Irving Center overnight following the study, as detailed in the study procedures section, for observation and supportive treatment as needed and discharged, if medically and psychiatrically cleared, the morning after ketamine administration. They will be followed up by telephone by research staff one day, one week, and again one month later, for any possible adverse outcomes related to administration of ketamine.

MRI scanning.

Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the machine if requested. We will screen subjects for heart pacemaker, or any other metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to remove any medicinal patches prior to the scanning session. For women of childbearing years, pregnancy testing will be conducted at screening and again on the day of the MRI. If the subject experiences unpleasant sensations or feels uncomfortable, the MR technologist will stop the scan immediately.

T1-weighted images from the MRS scan will be read by a neuroradiologist within one month of the scan, and a letter will be sent to the subject or a physician whom they designate whether the scan is normal or abnormal. Only the T1 weighted image from the first scanning session will be ready by a neuroradiologist. The PI or study physician will notify the subject or the subject's designated physician either in person or by

phone about any abnormalities. If any abnormalities are observed at the time of the scan by the technologist or an RA, that person will immediately let a study physician know, who will then determine the urgency of the situation and follow up with the subject or a neuroradiologist as needed. All abnormalities will be immediately reported to the PI.

Intravenous Catheters and Blood Sampling

Risks will be minimized having the placement of IVs done by a physician or nurse trained and certified in aseptic technique for catheter placement.

Interview and Neuropsychological Assessments

Risks are to be minimized by allowing as much flexibility in the interview process (e.g., doing the interview in several meetings, giving breaks) as possible. If subjects have emotional responses, appropriate psychological support is given. Most patients find the interviews and assessments helpful.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

Blood and urine samples, behavioral assessments, MRS acquisitions, and all other clinical/neuropsychological data will be obtained from the subjects for specific research purposes. Data will include self-report information, observer records, and physiological and behavioral information collected during test sessions. Each subject is assigned a unique ID and all data related to that subject is entered at the site by the site data entry personnel. The database files are stored on an encrypted, dedicated SQL Server, which has no access to the Internet. This database server is fully secured, requiring a secondary username and password to access any of the data located within the database server. NKI employs two Cisco 5520x Firewalls in an Active/Active scenario to protect the internal network and all servers from unauthorized access. Each Cisco firewall utilized AES-256 encryption algorithms to further protect the internal servers.

Hard copies of all information will be kept locked in confidential files at each site. Electronic transmission of information regarding a subject will only use the assigned identifier for that subject.

Data from medical records may also be used on occasion with appropriate permission (signed release from patient). The data manager will perform random data audits to further ensure the integrity of the data. Server backups of all study databases are performed nightly and encrypted using our backup software to LTO-5 tapes. Every morning, these tape backups are removed from the Computing Center and relocated to a separate building (in a secured room) located on the NKI campus. For archival purposes, database copies are encrypted and stored on DVD's and stored separately in a fire-proof, secured cabinet. NKI also employs an off-site, third-party backup provider to store our encrypted tape backups in their climate-controlled, secured vault for seven years.

NIMH has recently implemented a policy that allows for the sharing of mental health research data. NIMH has created data repositories to support the submission and sharing of this research data with the expectation this provides a valuable scientific resource. NKI will be responsible for bi-annual data submissions to the National Database for Clinical Trials (NDCT) on a timetable established by this repository. All subject data must be de-identified and each subject will be assigned a separate identifier to remove any possibility that "the identities of subjects cannot be readily ascertained or otherwise associated with the data by the repository staff or secondary data users." (45 CFR, 46.102).

To accomplish this, a Globally Unique Identifier (GUID) will be assigned to each subject. This process will be conducted by NKI using a national database called a GUID Tool. To submit to the GUID Tool and obtain this unique identifier, NKI needs the following information per subject: first name, last name, middle name (if applicable), month of birth, day of birth, year of birth, physical sex at birth, name of city/municipality where subject was born. This information will be collected by the site and entered into the study database. NKI will communicate with the GUID Tool and a GUID will be generated and entered into the study database for that specific subject. Once that is done, the personal information will be deleted from the study database.

Further Protection against Risk:

In the informed consent form, subjects will be told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff, with one exception: state or federal regulatory personnel and legal advocacy organizations authorized by law will have access to review records. Data collected with identifying information will be stored in locked cabinets or in password-protected computer files. Subject identity will not be revealed in the presentation or publication of any results. All staff working on the project will be educated about the importance of strictly respecting patient confidentiality.

Of note, the study described in this protocol is will be done independently of similar protocols being performed at Yale and UC Davis, all of which are part of Dr. Lieberman's FAST consortium (RFMH is the coordinating site). However, no human subjects work at any other site will be performed by investigator's of this protocol, nor vice versa. NKI will be the common data management site for all three sites. Therefore, any data from this site that is discussed with other sites will be fully de identified.

James Robinson, M. Ed. will serve as the Director of the Data Management Center. Mr. Robinson is uniquely qualified to lead the clinical research informatics and data management for this initiative. He possesses all of the requisite skills and expertise. Mr. Robinson has spent his entire career providing clinical research support services. He has over thirty five years of experience in clinical research data management, informatics, quality assurance, and study monitoring. He is the Director of the Information Sciences Division for the Research Foundation for Mental Hygiene at the Nathan S. Kline Institute. He is also the Director of Clinical Research Informatics and Data Management at the Center for Health Informatics and Bioinformatics, New York University Langone Medical Center. Mr. Robinson is currently the Director of Data Management Centers for five multisite clinical research studies including the 35 site Feinstein

Recovery after Initial Schizophrenic Episode (RAISE) study funded by the National Institute for Mental Health.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits to the subjects other than they will receive a complete medical, neurological and psychiatric evaluation, and results will be communicated to them.

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.

Subjects will receive a compensation of $50 for the screening visit and $300 for completion of each scan day. If subjects are admitted for an overnight stay at the Irving institute, they will be compensated an additional $50. The maximum total amount they may receive for the whole study will be $700. The one subject who participates in the initial pilot scan may receive up to $400.

All subjects may also be compensated for local transportation.

If a subject agrees to come in as a standby subject, he/she will receive a check or cash for $50. If a subjects comes in as a standby subject and is asked to participate in the scanning procedures, he/she will be paid according to the protocol. If a subject comes in as a standby subject multiple times, he/she will be paid $50 for each visit.

They will paid via check or cash. If by check they can expect to receive the check by mail within 4 to 6 weeks after the study.

If subjects do not complete the study procedures, payment is pro-rated to portions completed.

References

References

Bartha R, Williamson PC, Drost DJ, Malla A, Carr TJ, Cortese L, et al. (1997): Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy. Arch Gen Psychiatry. 54:959-965.

Carter CS, Minzenberg M, West R, Macdonald A, 3rd (2012): CNTRICS imaging biomarker selections: Executive control paradigms. *Schizophr Bull*. 38:34-42.

D'Souza DC, Singh N, Elander J, Carbuto M, Pittman B, Udo de Haes J, et al. Glycine transporter inhibitor attenuates the psychotomimetic effects of ketamine in healthy males: preliminary evidence. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012 Mar;37(4):1036-46.

de la Fuente-Sandoval C, Leon-Ortiz P, Favila R, Stephano S, Mamo D, Ramirez-Bermudez J, et al. (2011): Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. Neuropsychopharmacology. 36:1781-1791.

De Simoni S, Schwarz AJ, O'Daly OG, Marquand AF, Brittain C, Gonzales C, et al. (2013): Test-retest reliability of the BOLD pharmacological MRI response to ketamine in healthy volunteers. Neuroimage. 64:75-90.

First MB, Spitzer RL, Gibbon M, and Williams JBW (1996): Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington D.C.: American Psychiatric Press, Inc.

Herman EJ, Bubser M, Conn PJ, Jones CK (2012): Metabotropic glutamate receptors for new treatments in schizophrenia. Handb Exp Pharmacol.297-365.

Homayoun H, Moghaddam B (2007): NMDA Receptor Hypofunction Produces Opposite Effects on Prefrontal Cortex Interneurons and Pyramidal Neurons. J Neuroscience. 27:11496-11500.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al. (2008): Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 371:1085-1097.

Kantrowitz JT, Javitt DC (2009): Glutamatergic Approaches to the Conceptualization and Treatment of Schizophrenia. In: Javitt DC, Kantrowitz JT, editors. Handbook of Neurochemistry and Molecular Neurobiology 3rd Edition. New York City: Springer.

Kegeles, L. S., Abi-Dargham, A., Zea-Ponce, Y., Rodenhiser-Hill, J., Mann, J. J., Van

Heertum, R. L., et al. (2000). Modulation of amphetamine-induced striatal dopamine

release by ketamine in humans: implications for schizophrenia. Biol Psychiatry, 48(7), 627-640.

Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, et al. (2012): Elevated prefrontal cortex gamma-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Arch Gen Psychiatry. 69:449-459.

Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O, et al. (2002): NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. Synapse. 43:19-29.

Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S, et al. (2011): A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. J Clin Psychopharmacol. 31:349-355.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers M, Jr., Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of General Psychiatry. 1994;51(3):199-214.

Levine J, Schooler NR (1986): SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 22:343-381.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. (2005): Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New England Journal of Medicine. 353:1209-1253.

McNair DM, Lorr M, Droppleman LF (1981): Manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Service.

Nurnberger JI, Jr., Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. (1994): Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry. 51:849-859; discussion 863-844.

Overall JE, Gorham DR (1962): The brief psychiatric rating scale. Psychol Reports. 10:799-812.

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. (2007): Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med. 13:1102-1107.

Ragland, J.D., et al., Relational and Item-Specific Encoding (RISE): task development and psychometric characteristics. Schizophr Bull, 2012. 38(1): p. 114-24.

Theberge J, Bartha R, Drost DJ, Menon RS, Malla A, Takhar J, et al. (2002): Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. Am J Psychiatry. 159:1944-1946.

Théberge J, Williamson KE, Aoyama N, Drost DJ, Manchanda R, Malla AK, et al. (2007): Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. Br J Psychiatry. 191:325-334.

Zarate CA, Jr., Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload a copy of Certificate of Confidentiality
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study