Study Title: Biomarkers of Conversion Risk and Treatment Response in Early-Stage Schizophrenia

NCT: 03323437

NYSPI IRB #: 7474

Version date: April 27, 2023

**New York State Psychiatric Institute**

# Institutional Review Board

April 27, 2023

**To**: Dr. Lawrence Kegeles

**From**: Dr. Agnes Whitaker, IRB Co-Chair
Dr. Richard Foltin, Interim IRB Co-Chair

**Subject**: Approval Notice: Continuation Expedited per 45CFR46.110(b)(1)(f) Category 8c

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Your protocol # **7474** entitled: **BIOMARKERS OF CONVERSION RISK AND TREATMENT RESPONSE IN EARLY-STAGE SCHIZOPHRENIA-FIRST EPISODE STUDY** Protocol version date 04/27/2023 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **May 1, 2023 to April 30, 2024.**

**Consent requirements:**
√ Not applicable: Data Analysis Only
☐ 45CFR46.116 (f)(3) waiver of consent for medical record review
☐ 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.

AHW/RWF/alw

Signed copy on file at IRB

Protocol Title:
**Biomarkers of Conversion Risk and Treatment Response in Early-Stage Schizophrenia-First Episode Study**

Version Date:
**04/27/2023**

Protocol Number:
**7474**

First Approval:
**05/30/2017**

Expiration Date:
**04/30/2024**

Contact Principal Investigator:
**Lawrence Kegeles, MD**
**Email: lsk5@columbia.edu**
**Telephone: 646-774-5560**

Co-Investigator(s):
**Roberto Lewis-Fernandez, MD**
**Ragy Girgis, MD**

Research Chief:
**Lawrence Kegeles, MD**

## 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 with modifications

## Department & Unaffiliated Personnel

### Department

**What Department does the PI belong to?**
Translational Imaging
**Within the department, what Center or group are you affiliated with, if any?**
Translational Imaging

### 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.**

Dikoma Shungu PhD - Cornell University

Dr. Shungu's roles, as contact PI and project physicist, will be: overall study oversight as the awardee institution, with duties related to human subjects research limited to (a) obtaining de-identified imaging and clinical data from NYSPI; (b) processing imaging data from NYSPI; (d) overseeing/updating/ troubleshooting MRI data acquisition; and (e) submitting data from NYSPI twice per year to the NIMH Data Archive. Dr. Shungu will not be in contact with patients but will have access to information to the extent described above (blinded to diagnosis for the purpose of data analysis). Also in cases of serious adverse event, he will have access to the identity of the subject and have knowledge of any remedial action taken, for reporting to both the Cornell IRB and NIMH. In addition, since adverse events at NYSPI will need to be conveyed to the study's DSMB at Weill Cornell by Dr. Shungu, he will be informed of adverse events.

## Amendment

**Describe the change(s) being made**
Change status to data analysis only.
**Provide the rationale for the change(s)**
Enrollment has been completed.
**Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects**
No change.
**Comment on if the proposed change(s) require a modification to the Consent Form (CF)**
No change.

## 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.**

Recruitment has proceeded on schedule and uneventfully until it was slowed by the COVID pandemic. Enrollment has now been completed.

## 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)**
(automatic from NIH)

## Overall Progress

**Approved sample size**
60
**Total number of participants enrolled to date**
41
**Number of participants who have completed the study to date**
21
**Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?**
No
**Comments / additional information**
NA

## Sample Demographics

**Select the # of samples applicable**

Yes
**Specify population**
Medication-free schizophrenia subjects
**Total number of participants enrolled from this population to date**
21
**Specify population #2**
Healthy controls
**Total number of participants enrolled from this population to date**
20
**Gender, Racial and Ethnic Breakdown**
Sample 1: Medication Free SZ Subjects 9 Females, 12 Males Breakdown: Females: 3 Black, Non-Hispanic 3 White, Non-Hispanic 1 Black, Hispanic 2 Native Hawaiian or Other Pacific Islander, Hispanic Males: 1 Black, Hispanic 6 Black, Non-Hispanic 3 White, Hispanic 2 White, Non-Hispanic Sample 2: Healthy Controls 11 Females, 9 Males Breakdown: Females: 2 White, Non-Hispanic 4 Black, Non-Hispanic 3 Asian, Non-Hispanic 1 Black, Hispanic 1 Other, Hispanic Males: 3 White, Non-Hispanic 3 Black, Non-Hispanic 1 White Hispanic 2 Unknown, Hispanic

**Summary of Current Year's Enrollment and Drop-out**

**Number of participants who signed consent in the past year**
3
**Number of participants currently enrolled**
0
**Did the investigator withdraw participants from the study?**
Yes
**Circumstances of withdrawal:**
One participant (patient) was found in the course of screening not to meet study criteria and was withdrawn by the investigator.
**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**
✓ Internet-based Data Collection or Transmission
✓ MRI
✓ Neuropsychological Evaluation
✓ Psychiatric Assessment

## Population

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

✓ Adults who may have impaired decision-making ability
✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Individuals with Psychosis
✓ Inpatients

Protocol Title:
**Biomarkers of Conversion Risk and Treatment Response in Early-Stage Schizophrenia-First Episode Study**

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**05/12/2022**

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**7474**

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**05/30/2017**

Expiration Date:
**04/30/2023**

Contact Principal Investigator:
**Lawrence Kegeles, MD**
**Email: lsk5@columbia.edu**
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Co-Investigator(s):
**Roberto Lewis-Fernandez, MD**
**Ragy Girgis, MD**

Research Chief:
**Lawrence Kegeles, MD**

## 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 proposing an amendment only to an existing protocol

## Department & Unaffiliated Personnel

### Department

What Department does the PI belong to?
Translational Imaging
Within the department, what Center or group are you affiliated with, if any?
Translational Imaging

### 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.

Dikoma Shungu PhD - Cornell University

Dr. Shungu's roles, as contact PI and project physicist, will be: overall study oversight as the awardee institution, with duties related to human subjects research limited to (a) obtaining de-identified imaging and clinical data from NYSPI; (b) processing imaging data from NYSPI; (d) overseeing/updating/ troubleshooting MRI data acquisition; and (e) submitting data from NYSPI twice per year to the NIMH Data Archive. Dr. Shungu will not be in contact with patients but will have access to information to the extent described above (blinded to diagnosis for the purpose of data analysis). Also in cases of serious adverse event, he will have access to the identity of the subject and have knowledge of any remedial action taken, for reporting to both the Cornell IRB and NIMH. In addition, since adverse events at NYSPI will need to be conveyed to the study's DSMB at Weill Cornell by Dr. Shungu, he will be informed of adverse events.

## Amendment

Describe the change(s) being made

This amendment request is a response to IRB review comments of May 9, 2022 (IRB email_to_lsk5@columbia.edu, attached) regarding a request for amendment to this protocol.

Review comments and our responses are
**1) The COPE website ad references a link for screening. This should be discussed in the Recruitment Procedures section of the PSF and the Study Procedures under the subheading Screening. State where the link leads. If it take the individual to a site that is NOT HIPAA-compliant, please consult with Christopher Stanley and provide that correspondence.**

Response: The link will lead to a previously approved RecruitMe advertisement. The link and its destination are now discussed in the PSF under Recruitment Procedures and Study Procedures, Screening.

**2) The ad should reference "research study" rather than simply "study."**

Response: The requested change has been made in the ad.

We submitted the amendment request below on April 24, 2022 and received queries from the IRB to which we are responding here.

- *** If only recruitment material is submitted for approval, it should be submitted via FAST TRACK in

PRISM rather than via an amendment. Please email IRBMail to let us know if the Amendment should be withdrawn so a Fast Track can be submitted.

Please see attached email which replied that an amendment is necessary since the recruitment material is requested to be posted on a new venue. The new venue is specified in the PSF under Recruitment Procedures.

- *** Please indicate if you're submitting the recruitment ad for the new approval dates of 5/1/2022 through 4/30/2023.

Please see attached email which replied that the approval dates sought are for the new approval dates for this protocol.

Amendment request of April 24, 2022:

We are requesting approval to place a previously approved recruitment ad, attached, on the COPE website. To accommodate the website venue, we are adding the language, “Please follow this link to see if you are eligible to participate,” which will be associated with a hyperlink to a redcap survey that confirms the person meets the basic criteria for the study, i.e. the age range and whether they are having unusual thoughts/experiences.

Provide the rationale for the change(s)
to facilitate recruitment
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
No effect
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
None required

## Procedures

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

✓ Internet-based Data Collection or Transmission
✓ MRI
✓ Neuropsychological Evaluation
✓ Psychiatric Assessment

## Population

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

✓ Adults who may have impaired decision-making ability
✓ Medically and Psychiatrically Healthy Subjects
✓ Adults

✓ Individuals with Psychosis
✓ 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
Federal
Institute/Agency
NIMH
Grant Name
Biomarkers of Conversion Risk and Treatment Response in Early-Stage Schizophrenia
Grant Number
R01 MH110270
Select one of the following
Multicenter (NYSPI is a participating site)
Business Office
Other
Name
RFMH and Columbia
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
From
Name institution(s)

Weill Cornell Medical Center, where contact PI of the grant is Dr. Dikoma Shungu.
Dr. Shungu's roles will be: (a) overall study oversight as the awardee institution and location of contact PI; (b) to obtain de-identified imaging and clinical data from NYSPI; (c) to process imaging data from NYSPI; (d) to oversee/update/troubleshoot MRI data acquisition; and (e) submit data from NYSPI twice per year to the NIMH Data Archive.

**Please note that Dr. Kegeles, the PI of the IRB protocol, has two roles on the grant: multi-PI of the grant and PI of the CU subaward.**

## Study Location

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

## Lay Summary of Proposed Research

Lay Summary of Proposed Research
Schizophrenia (SZ) is a highly debilitating neuropsychiatric disorder of young adulthood onset and a leading cause of disability worldwide. While treatments delivered at early stages of the disorder may be effective at reducing psychosis or altering the course of the disease, there are currently no biomarkers capable of identifying subjects in early stages of SZ who are likely to respond to treatment and would be good candidates for available proactive, symptomatic or future disease-modifying treatments; or those who would not respond and can be spared unnecessary medication exposure. The lack of these vitally important biomarkers provides a compelling rationale for the present multidisciplinary research project, which aims to develop and validate highly promising noninvasive and objective proton magnetic resonance spectroscopy (1H MRS)-based biomarkers for monitoring treatment response in early stages of SZ. In support of the viability of this overall objective is a large body of data, reported by the applicants and others, that show (a) that levels of glutamate (Glu) and - aminobutyric acid (GABA) – respectively, the major excitatory and inhibitory amino acid neurotransmitter systems - are abnormally elevated in medication-naïve and unmedicated first episode and chronic SZ patients; (b) that the effect of treatment with antipsychotic medications in these populations may be to lower or normalize brain levels of both Glu and GABA. To investigate the potential of these in vivo brain Glu and GABA abnormalities to serve as biomarkers of treatment response in early-stage SZ, the applicants propose to use 1H MRS to measure Glu and GABA levels in the largest cohort of medication-free SZ subjects to date, at baseline and following 4 weeks of antipsychotic treatment.

## Background, Significance and Rationale

Background, Significance and Rationale
Over the past 50+ years, several heuristic models of SZ pathophysiology have been proposed. None, however, has commanded more attention than the dopamine (DA) hypothesis (Carlsson and Lindquist 1963; Snyder 1976) which, in its classical formulation, posits that hyperactivity of DA transmission is responsible for at least some of the symptoms of the disorder. The ability of DA D2 receptor antagonists to ameliorate the positive symptoms of SZ, and of DA agonists to exacerbate these symptoms in patients and provoke

psychotomimetic symptoms in normal subjects, lent strong support to the DA hyperactivity hypothesis. However, despite its confirmation in vivo by neuroimaging in the late 1990s (Laruelle et al 1996; Abi-Dargham et al 1998; Laruelle and Abi-Dargham 1999; Breier et al 1997, 1998), the hypothesized striatal hyperdopaminergia in SZ could not account for the negative symptoms and cognitive impairment that contribute enormously to the long-term disability in the disorder (Davis et al 1991).

The hypothesis that SZ might be associated with deficiency in the function of the Glu N-methyl-Daspartate (NMDA) receptor addresses some limitations of the DA hyperactivity model (Javitt and Zukin 1991; Olney and Farber 1995; Tamminga et al 1995). In contrast to the DA agonists, which reproduce only the positive symptoms, it was observed that the Glu NMDA receptor antagonists phencyclidine (PCP) and ketamine could produce a number of both the positive and negative symptoms of SZ in normal subjects, as well as exacerbate these symptoms in patients (Javitt and Zukin 1991; Tamminga 1998; Coyle 1996; Krystal et al 1994; Krystal et al 1999). Therefore, the NMDA receptor hypofunction (NRH) hypothesis offered a very compelling pharmacological model of the illness, which more recent research has extended and shown to be associated with a hyperglutamatergic state (Moghaddam et al., 1997). In sum, the preceding considerations lend support to the emerging neurochemical hypothesis of SZ that integrates the Glu or NRH model and GABA dysfunction with the DA model (Olney and Farber 1995; Carlsson et al 2001; Lodge and Grace 2007). We will assess treatment response to DA-based antipsychotics in medication-free SZ subjects through measurements of cortical Glu and GABA levels, which have the potential to demonstrate the proposed MRS biomarkers across both dopaminergic and glutamatergic/GABAergic components of intervention efficacy in SZ to provide further support for this neurochemical model.

The overall objective is to develop and validate in vivo proton magnetic resonance spectroscopy (1H MRS) measures of the amino acid neurotransmitters, GABA and glutamate, as reliable and objective biomarkers of full psychosis, as well as “target engagement” biomarkers for monitoring the therapeutic response in schizophrenia, identifying novel glutamate- and GABA-based treatment targets and/or advancing our understanding of the underlying brain mechanisms. Such biomarkers could enable the objective assessment of disease progression and therapeutic response to existing and emerging treatments.

## Specific Aims and Hypotheses

Specific Aims and Hypotheses
pastingAim 1 To measure DCA and MPFC GABA and Glu levels in 60 medication-free SZ subjects across two study sites at baseline and then following 4 weeks of treatment with risperidone, an approved second-generation antipsychotic, according to standard of care in comparison with 30 age- and sex-matched healthy controls across two study sites at baseline and at 4 weeks.

Aim 2 Clinical Correlations: To confirm that neurotransmitter levels will correlate with clinical status and antipsychotic treatment/response as assessed by a battery of established clinical ratings.

## Description of Subject Population

**Sample #1**

Specify subject population
Medication-free SZ subjects
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
18-35

**Sample #2**

Specify subject population
Healthy Controls
Number of completers required to accomplish study aims
15
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population
18-35

Gender, Racial and Ethnic Breakdown
Population Gender
Females 35%
Males 65%

Race: African American 35% Caucasian 40%, Asian 10%, Mixed 15%

Ethnicity: Hispanic 30%, Non Hispanic 70%
Description of subject population
As above.

## Recruitment Procedures

Describe settings where recruitment will occur
Subjects will be recruited through: (a) word-of-mouth, (b) referral from medical and mental health professionals, (c) publicity about the study, including articles in local newspapers and magazines, appearances on local radio and television shows, etc., leading to self-referral of prospective patients, (d) advertisements placed in local media/Internet (Craigslist, Reddit, RecruitMe, **the COPE program website,** and Schizophrenia.com, Google Ads, Instagram, Twitter, Facebook), as well as from e) clinics at NYSPI, (f) Lieber clinic. **The ad on the COPE website will contain a link to the RecruitMe ad.** Our recruitment efforts will target community SZ and control samples by advertising in community newspapers (e.g., the Village Voice) as well as extensive outreach. The nature of the procedures and the alternatives to study

participation will be discussed with each subject prior to obtaining written informed consent. A multidisciplinary team including at least one psychiatrist not associated with the study will review the eligibility of the patients, with special attention to the ability of the patient to understand and evaluate the risks associated with the study (capacity evaluation). The evaluation of the psychiatrist not involved in the study is documented in the chart.
How and by whom will subjects be approached and/or recruited?
See above.
How will the study be advertised/publicized?
See above.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
No

## Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Participants will be recruited from other research studies within our research Area at NYSPI (Area Psychotic Disorders).

## Inclusion/Exclusion Criteria

Name the subject group/sub sample
Medication-free SZ subjects
Create or insert table to describe the inclusion criteria and methods to ascertain them

| Inclusion Criteria | Method of Ascertainment |
|---|---|
| 1. Male or females between the ages of 18-35 | History |
| 2. less than five years (<60 months) of active DSM diagnosis of schizophrenia, schizophreniform, or schizoaffective | SCID/Interview |
| 3. Capacity for provide informed consent | Interview |
| 4. No major medical or neurological illness | Physical exam, laboratory tests, EKG |
| 5. Medication free (3 weeks without antipsychotic medications) | Interview |

3 weeks without antipsychotic medications has become an accepted duration to be considered medication free in both neuroreceptor imaging and MR Spectroscopy studies. Please see below for citations that use this accepted 3 week duration:

Laruelle, M., Abi-Dargham, A., Van Dyck, C. H., Gil, R., D'Souza, C. D., Erdos, J., ... & Baldwin, R. M. (1996). Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proceedings of the National Academy of Sciences, 93(17), 9235-9240.

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L. S., ... & Gorman, J. M. (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proceedings of the National Academy of Sciences, 97(14), 8104-8109.

Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, Hwang D-R, Huang Y, Haber S, Laruelle M: Increased synaptic dopamine in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry 2010;67(3):231-239

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

| Exclusion Criteria | Method of Ascertainment |
|---|---|
| 1. Current alcohol or drug abuse (<1 month) or substance dependence (<6 months) or substances used within one day of the imaging study | History, SCID, Urine toxicology |
| 2. Pregnant or lactating women or women of child-bearing potential, who are either not surgically-sterile or, for outpatients, not using appropriate methods of birth control (i.e. condom plus diaphragm with spermicide, condom plus spermicide, intrauterine device, birth control pills, or abstinence). | Serum HCG, assessment |
| 3. IQ<70 | WTAR <6 if mental retardation is suspected |
| 4. Acute risk for suicide or violence | Interview and history |
| 5. Presence of pacemaker or any metallic objects in the body that would interfere with the MRS or cause MRI safety problems | Interview and history |
| 6. Claustrophobia | Interview |
| 7. Any organic brain disorder (including epilepsy, mental | Interview, |

| | |
|---|---|
| retardation, or a medical condition whose pathology or treatment would likely alter the presentation or treatment of SZ | physical exam, laboratory tests |
| 8. Individuals on anti-epileptic medications (e.g., valproate, carbamazepine) that may affect GABA or Glu | Interview |
| 9. Unstable medical or neurological condition | Interview, physical exam, laboratory tests |
| 10. DSM-V diagnosis of bipolar disorder I | Interview |
| 11. DSM-V diagnosis of major depression with psychotic features | Interview |
| 12. History of non-response to or non-tolerance of Risperidone | Interview and History |

## Inclusion/Exclusion Criteria #2

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

| Inclusion Criteria | Method of Ascertainment |
|---|---|
| 1. Male or females between the ages of 18-35 | History |
| 2. Capacity for provide informed consent | Interview |
| 3. No major medical or neurological illness | Interview |

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

| Exclusion Criteria | Method of Ascertainment |
|---|---|
| 1. Current alcohol or drug abuse (<1 month) or substance dependence (<6 months) or substances used within one day of the imaging study | History, SCID, Urine toxicology |
| 2. Pregnant or lactating women or women of child-bearing potential, who are either not surgically-sterile or, for outpatients, not using appropriate methods of birth control (i.e. condom plus diaphragm with spermicide, condom plus | Urine pregnancy test, assessment |

| | |
|---|---|
| spermicide, intrauterine device, birth control pills, or abstinence). | |
| 3. IQ<70 | WTAR<6 if mental retardation is suspected |
| 4. Acute risk for suicide or violence | Interview and history |
| 5. presence of pacemaker or any metallic objects in the body that would interfere with the MRS or cause MRI safety problems | Interview and history |
| 6. Claustrophobia | Interview |
| 7. History of psychotropic medication use such as antipsychotics or antidepressants | Interview and history |
| 8. Any first-degree family history of psychotic illness | Interview and history |
| 9. Personal history of any DSM Axis I disorder | Interview, SCID, history |
| 10. Individuals on anti-epileptic medications (e.g., valproate, carbamazepine) that may affect GABA or Glu | Interview |
| 11. Unstable medical or neurological condition | Interview |
| 12. Any organic brain disorder (including epilepsy, mental retardation, or a medical condition whose pathology or treatment would likely alter the presentation or treatment of SZ | Interview |

## 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?
No
Describe procedures used to obtain consent during the screening process
The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential subjects across several sessions. The number of sessions over which this information will be provided will depend on how well the subject understands and retains the information. The process begins with the subject initiating contact via telephone. The research staff provide a brief description of the study. Thereafter, potentially eligible candidates are scheduled for a face-to-face interview. The study procedures will be described as a research tool with potential to enhance our knowledge about treatments for schizophrenia. Subjects will also 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 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 subject did not fully understand the study, the PI may decide that the subject is not suitable for participation. If the subject is suitable and 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 given the opportunity to withdraw from the study prior to analysis of their data. Following the resolution of any questions, the subjects will be asked to sign the consent form, if he/she agrees to participate.
Remote/virtual Procedures: Remote procedures will be similar to in person procedures except that we will use Redcap to obtain signed consent (using the e signature feature) on the consent forms and HIPAA forms. This may occur by either phone or video. If a subject is unable to use Redcap for any reason, we will accept a consent form that is signed and scanned and sent to us. 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.

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 across several sessions. The number of sessions over which this information will be provided will depend on how well the subject understands and retains the information. The process begins with the subject initiating contact via telephone. The research staff provide a brief description of the study. Thereafter, potentially eligible candidates are scheduled for a face-to-face interview. The study procedures will be described as a research tool with potential to enhance our knowledge about treatments for schizophrenia. Subjects will also 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 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 subject did not fully understand the study, the PI may decide that the subject is not suitable for participation. If the subject is suitable and 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 given the opportunity to withdraw from the study prior to analysis of their data. Following the resolution of any questions, the subjects will be asked to sign the consent form, if he/she agrees to participate.
Remote/virtual Procedures: Remote procedures will be similar to in person procedures except that we will use Redcap to obtain signed consent (using the e signature feature) on the consent forms and HIPAA forms. This may occur by either phone or video. If a subject is unable to use Redcap for any reason, we will accept a consent form that is signed and scanned and sent to us. 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.

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

## Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Califano, Allegra
Cohen-Romano, Carol
Girgis, Ragy, MD
Hesson, Hannah, BA
Kegeles, Lawrence, MD
Type in the name(s) not found in the above list

Allegra Califano, **Hannah Hesson, and Carol Cohen Romano** will discuss and document consent only with healthy control participants.

Drs. Girgis and Kegeles will discuss and document consent with any potential participants.

## 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?
Yes
Methods/procedures for capacity assessment

Subjects who do not have decision-making capacity will not be recruited for this study. Capacity will be assessed independently by an independent clinician who is not a member of the research team. Any licensed psychiatrist or psychologist (MD/PhD) who works in the New York State Psychiatric Institute and has completed CITI training may assess capacity.

Remote/virtual Procedures: Remote procedures will be similar to in person procedures except that we will use Redcap for the patient and the independent clinician performing capacity evaluation. This may occur by either phone or video. If a patient is unable to use Redcap for any reason, the clinician performing capacity evaluation will use phone to contact the patient and will access Redcap for signature. As with the consent procedures we will discuss with the patient 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.

## Study Procedures

Describe the procedures required for this study
All subjects will undergo the following procedures:

- Screening: **Initial basic study criteria screening questions (age range, presence of symptoms or previous diagnosis) may be asked during recruitment prior to the initial screening visit, such as on the RecruitMe website.** Subjects will be initially evaluated with a medical and psychiatric history and patients with schizophrenia will have a physical examination. All participants will have the option of a COVID-19 saliva test during their first visit. A urine toxicology will be obtained to rule out substance use and a urine pregnancy test on females. For patients with schizophrenia, we will also obtain an EKG and blood for TSH, electrolytes, liver and kidney function, and CBC, as well as a serum HCG in women. To obtain a research diagnosis, the SCID (Spitzer et al 1992) is completed by a trained and reliable interviewer followed by a consensus conference. We will not repeat screening procedures (i.e., EKG or lab tests) that have been performed within 90 days so as to decrease burden to patients.

- After screening, all subjects will receive the full battery of assessments including the MATRICS, CGI S and I, GAF, Hollingshead, Work as Meaning Inventory (WAMI), Fagerstrom test of nicotine dependence, and UPSA as described below in the assessments section.

Additional information is collected through the Positive and Negative Syndrome Scale (PANSS) (Kay 1987), the Clinical Global Impression (CGI) scale, and the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976), current and past medications log, medical history, previous treatment history, Substance Use Self Report (AUS/DUS), WTAR, Global Assessment of Functioning (GAF), and the Edinburgh inventory of handedness (Oldfield 1971). Subjects will be assessed with the above measures at baseline (all participants) and at 4 weeks (patients only), with the exception of the Edinburgh inventory of handedness and WTAR which will only be obtained at baseline, and the AIMS, which will be administered only to patients.

- All subjects will receive a baseline MRI scan with 1H MRS to measure Glu and GABA levels. Images will be acquired on the 3T scanner at NYSPI. During this MRI session, which will last up to 2 hours, patients will receive structural scans as well as MRS at baseline.

- After completing the baseline MRI scan, medication free SZ subjects will be started on the antipsychotic medication risperidone, and will receive antipsychotic medication (Risperidone) for 4 weeks. They will be treated naturalistically by a study physician. Risperidone is FDA approved for the treatment of acute and maintenance therapy of schizophrenia. Risperidone has been documented to be efficacious in the treatment of schizophrenia as well as other psychotic disorders. This medication represents the standard of care in the community and has the leading market share by prescription of all antipsychotics (1998 Medicaid Data). For inpatients on 5-South the attending psychiatrist, in consultation with the study physicians, will provide the medication treatment. For outpatients, the study physicians will provide the medication treatment.
- During the treatment period, all patients will meet with a study physician, once per week (about 3 times total). The visit will include assessment for therapeutic effects and adverse events using the PANSS, AIMS, CGI, and GAF.

- At 4 weeks, medication free SZ subjects will be assessed with the MATRICS and UPSA, and will undergo the same MRI with 1H MRS procedures as at baseline to measure Glu and GABA levels.

Some visits may be conducted remotely using the telephone or HIPAA-compliant video teleconferencing. When available we will use recent lab test, physical exam, and EKG results for patient screening. We will have study medications sent from the research pharmacy to patient participants whenever possible to minimize onsite visits. For patients who need to come onsite for labs, physical, and EKG, we will schedule the first MRI on the same day and then start study medications after these results are obtained and patients are cleared for medication administration.

All procedures other than the MRI scans can be conducted remotely. However, if a patient does not have recent physical exam, EKG, and laboratory test information available, or lacks phone or internet access suitable for our screening or medication evaluations, or lacks a suitable address for taking delivery of study medication, in-person visits would become necessary. Time required for these visits would be

Screening Visit:
- Physical exam, EKG, lab tests.....30 min
- SCID, PANSS, Medical history, GAF, CGI, AIMS, MATRICS, WTAR, Edinburgh Handedness, Hollingshead, WAMI, MRI Metal Screener. .....90 min

Weekly medication visits/evaluations (3 visits). .....15 min each

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.

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.

Monitoring of Patients for Clinical Worsening

Monitoring of patients will occur at the weekly in-person or remote evaluation and medication distribution visits with the study physician described above in the study procedures. These visits will include, as noted above, clinical evaluation as well as assessment for therapeutic effects and adverse events using the PANSS, AIMS, CGI, and GAF. In addition, the study physician's contact information will be provided with instructions to call in case of worsening clinical condition or subjective distress or discomfort at any time between weekly visits.

Criteria for Early Discontinuation

A CGI-S or CGI-I of > 5 will trigger an evaluation for removal from the study.
Criteria for withdrawing a patient from the study at any time:
- Clinically significant adverse events, which would be inconsistent with continuation in the study
- Clinical judgment of the investigator, based on for example, patients being unable or choosing not to comply with the study procedures
- Withdrawal of consent and/or patient decision
- Pregnancy
- Any evidence of suicidality/homicidality
- A Change of +2 in the CGI scale or CGI-S or CGI-I of 6 or 7

Specific Withdrawal Criteria for the Medication Free period include:
A patient will be discontinued from the antipsychotic-free period if he or she experiences any worsening of symptoms and/or represents a risk for self-harm or violence as evidenced by: (1) observed or reported aggressive/self-injurious behavior; (2) agitation; or (3) subjective distress/discomfort despite clinical intervention, or (4) an increase in CGI-S of 2+ or a CGI-S or CGI-I score of 6 or 7.

If any subject suffers a serious adverse event, such as a suicide attempt or an episode of agitation or violence towards others, between diagnosis and initiation of imaging, it will result in stopping the study and making a report to the IRB and DSMB for evaluation.

You can upload charts or diagrams if any

## Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
All recruited subjects will undergo the following battery of assessments to derive the clinical measures to be correlated with the proposed neuroimaging measures: (a) Demographic and clinical characteristics: Patients will be assessed for age, sex, ethnicity, medication status (antidepressant/anxiolytic yes/no; antipsychotic yes/no; exclusionary if 'yes' at entry for all groups), and drug use within past month (i.e. cannabis yes/no, 'yes' will be exclusionary; tobacco yes/no, 'yes' will not be exclusionary). Urine toxicology will confirm recent drug use status. (b) Positive and Negative Symptoms: Positive and Negative Syndrome Scale (PANSS) Kay et al., 1987) (15 minutes) measures positive and negative symptoms and general psychopathology. (c) Neuropsychology: Patients will also be assessed with the Global Assessment of Functioning (GAF) scale (Jones et al 1995; 3 min), which is a clinician-rated measure of symptom severity and role function; the CGI-Severity and –Improvement Scales (CGI-S and CGI-I; 3 min) (Guy 1976) which are clinician-rated measures of overall clinical status, and the University of California Performance-based Skills Assessment (UPSA; 10 min) scale (Patterson et al 2001). Cognition will be assessed using the MATRICS consensus cognitive battery (Green and Nuechterlein 2004; 90 min).
The Abnormal Involuntary Movement Scale (AIMS) (Guy 1976), current and past medications log, medical history, previous treatment history, Substance Use Self Report (AUS/DUS), WTAR, Edinburgh inventory of handedness (Oldfield 1971), and the MRI Metal Screener are also used. The Hollingshead will be performed for socioeconomic status (Hollingshead 1975; 5 minutes) as will the WAMI (Work and Meaning Inventory, 10 minutes) and the Fagerstrom test for Nicotine Dependence (Heatherton et al., 1991) will be performed as a measure of nicotine dependence.
Please attach copies, unless standard instruments are used

## Research Related Delay to Treatment

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

For patients with SZ, participation is associated with delays in initiating antipsychotic treatment from 1 to 10 days, depending on scheduling of MRI/MRS sessions. Absence of antipsychotic medication treatment can result in continuation or worsening of psychotic symptoms, which might include hallucinations, delusions, thought disorder, anxiety, depression, suicidality, violence toward self and others, and increased risk of accidents. The precautions needed to maintain patients antipsychotic-free until the initial MRI/MRS sessions are completed are adequate selection and clinical care. We will exclude patients with suicidal or homicidal ideation, history of violence or behavioral dyscontrol, and patients too impaired to give informed consent. However, if any medication-free patient does deteriorate, they will immediately be offered inpatient care. Inpatients will be monitored very closely by nursing staff and evaluated daily by a physician. Medications will be started immediately if it is felt that the continuation of the study might be unsafe. Specifically, emergence of suicidal or homicidal ideation, risk of elopement, risk of violence or decrease in the ability of the patient to understand the nature of the study will automatically result in appropriate treatment and exclusion from the study. At any time, the patient can request to withdraw from the study and to initiate antipsychotic treatment.

Medication free SZ subjects will not be enrolled if they are currently taking any antipsychotic medications. Every effort will be made to ensure the maximum delay to any treatment would be less than 10 days (usually between 1-5 days) from consenting procedures, depending on scheduling of MRI/MRS sessions.

Maximum duration of delay to standard care or treatment of known efficacy
Medication free SZ subjects: 1-10 days between consent to treatment as above.
Treatment to be provided at the end of the study
Upon completing the protocol (or if a subject drops out or is withdrawn from the study) all subjects will have the option of receiving treatment at the Lieber Schizophrenia Research Clinic or remain with their current treatment physician or clinic. The Lieber Clinic offers treatment free of charge to individuals who participate in research study (medications are not free). It is anticipated that most of the subjects in the current study will either start out as subjects in the Lieber clinic or be transitioned to the Lieber clinic during the course of the study. For individuals who do not wish to receive follow-up treatment at the Lieber Clinic appropriate referrals will be provided.

## Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Venous blood sample
Blood sampling in the amount of 15 mL or 1 tablespoon for screening laboratory tests 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. Laboratory tests will not be repeated for patients whose clinical admission tests suffice for the screening.

MRI
1. There is a potential risk that confidential health information collected during the course of the study may be disclosed to others.
2. There is a potential risk that the participants may find exposure to the clinically sensitive questions, such as answering questions about symptoms distressful. They also may become anxious, bored, or fatigued.
3. There is a potential risk from participating in the magnetic resonance imaging (MRI).
a) MRI is not associated with any known adverse effects except for people with metal or magnetic implants(such as metallic clips in the brain, metal dust in eyes or cardiac pacemakers). Therefore, a subject would be excluded from the study if they had any of these devices or conditions. Careful screening and monitoring will be carried out to the time of initial eligibility screening and again at the MRI appointment to ensure safety.
b) The scan and/or lying still on the scanning table may become uncomfortable for some individuals. Individuals who get severely anxious when in enclosed places will probably find this to be a difficult procedure. For subjects who anticipate being anxious during the procedure but are still willing to attempt MRI scanning, an experienced MRI technician will be present to check in with the subjects periodically in order to ensure comfort or relieve possible fear of being in small enclosed spaces (claustrophobia). Other discomforts may include hearing different sounds during the MRI examination. At first, there will be a metallic tapping sound that lasts about 30 seconds. This happens while the equipment is being prepared for scanning. During the scanning, there will be a combination of rhythmic knocking sounds. These sounds are continuous, but are not harmful and earplugs will be provided. Fast imaging sequences may also have the

potential to induce peripheral nerve stimulation, which is described as a light touching or tingling sensation on the skin surface and may cause mild discomfort, but is not harmful. Rarely, this can be painful. Peripheral nerve stimulation is temporary and the sensations stop as soon as scanning has ended. Lastly, there is a small risk that cables and button response boxes could become heated. Subjects are urged to report any heating sensation or discomforts immediately. Subjects are provided with a means of alerting the staff about any discomfort, and can be removed from the MRI machine at any time.
c) The long term effects of being placed in a MRI are unknown, but there have been no reports of any ill long–term effects caused by magnets of the same or even higher strength, either here or elsewhere. Furthermore, the risks of MRI scanning to a fetus is unknown. Although no known risks are associated with pregnancy, we will not scan someone who is pregnant. We will require that women take a urinary pregnancy test (that will be provided prior to the scan in order to ensure that they are not pregnant. All screening results will be kept confidential.
d) Incidental MRI findings: Scans will be read by a neuroradiologist for incidental findings. If anything clinically significant is found, Dr. Ragy Girgis, MD will be notified immediately, and an appropriate clinical referral will be provided to the participant. Results of the MRI will be provided to the subjects by a COPE physician. Subjects can opt to receive a letter regarding the results of the MRI on the consent forms.

Treatment with Risperidone
Risperidone is a standard atypical antipsychotic medication, with proven efficacy for SZ, and is recommended as a first treatment for individuals with SZ (Buchanan et al 2009). Hence, it is an appropriate drug for patients entered into this study. Patients who do not do well or cannot tolerate doses of risperidone specified here or need adjunctive anticholinergic medication will be offered clinical treatment and be discontinued from the study. Patients will be informed before the study that although risperidone is an approved medication for treatment of their condition, it is not the only medication or necessarily the best medication for them. They will also be informed of potential adverse events associated with risperidone that include rare events of neuroleptic malignant syndrome and tardive dyskinesia and common reactions of somnolence, anxiety, extrapyramidal effects, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, diarrhea, weight gain, menstrual irregularity, and sexual dysfunction.

For patients with SZ, participation is associated with delays in initiating antipsychotic treatment of up to 10 days (usually 1 to 5 days), depending on scheduling of MRI/MRS sessions. Absence of antipsychotic medication treatment can result in continuation or worsening of psychotic symptoms, which might include hallucinations, delusions, thought disorder, anxiety, depression, suicidality, violence toward self and others, and increased risk of accidents. The precautions needed to maintain patients antipsychotic-free until the initial MRI/MRS sessions are completed are adequate selection and clinical care. We will exclude patients with suicidal or homicidal ideation, history of violence or behavioral dyscontrol, and patients too impaired to give informed consent. However, if any antipsychotic-naïve patient does deteriorate, they will immediately be offered inpatient care. Inpatients will be monitored very closely by nursing staff and evaluated daily by a physician. Medications will be started immediately if it is felt that the continuation of the study might be unsafe. Specifically, emergence of suicidal or homicidal ideation, risk of elopement, risk of violence or decrease in the ability of the patient to understand the nature of the study will automatically result in appropriate treatment and exclusion from the study. At any time, the patient can request to withdraw from the study and to initiate antipsychotic treatment.

Of note, no patients will be withdrawn from medication management solely for the purpose of research.

COVID-related Risks:
There is a risk of exposure to COVID when deciding to go out in public and travel for research.

Participating in MRI scans may involve some risk of exposure to COVID.

Describe procedures for minimizing risks
Protection against Risk:
1. Confidentiality will be maintained by assigning each subject a study number, and coding all data collected with that number. Neuroimaging data are collected on the scanner and sent directly to a secure neuroimaging server at NYSPI. Scan files are named without any identifying information. Only designated study personnel (PI and other study team members) could have access to these scanned files. All computer databases are password protected, and hard copies of all data and records will be stored in locked filing cabinets. The database will be secured with a password, and all computers with access to the data will be secured with passwords and locked screen savers. Any data transmitted across the internet between evaluators will be encrypted with passwords. No participant names or identifying information will be shared across the internet between researchers. Both NYSPI and Columbia's computer system, where the data will be stored, uses state-of-the-art network security systems. An actively managed firewall and intrusion detection system monitors and blocks all suspect inbound and outbound network traffic. In addition, for data security the University provides secure file servers with hourly snapshot back-ups and off-site file storage. All study personnel will be certified to conduct research with human subjects, and will be aware of the importance of maintaining strict confidentiality.
2. Furthermore, any distress will be minimized by having a study staff person monitor the subject's experiences during the study procedures. A member of the research team will be available to assist the subject if she or he becomes distressed by study procedures. In addition, participants will be told that they may decline to answer any questions or discontinue the study if they find procedures distressing. Study staff will consult about any possible serious adverse event with Dr. Ragy Girgis or Dr. Lawrence Kegeles immediately, and address patient safety. Participants will also be debriefed at the conclusion of the study and asked about any possible experiences of distress. If any distress is indicated, this feedback will be utilized to modify the study stimuli and/or study procedures to reduce distress.
3. Risks of MRI -- To minimize fatigue, boredom or frustration during clinical and neuropsychological assessments and MRI, subjects will be offered breaks or the option to divide the assessments into more than one session. Efforts will be made to ensure subjects are comfortable, including providing earplugs. All subjects will be instructed at the beginning of the scan to report any sensations or discomforts during the scan. An experienced MRI technician will periodically check in with subjects in order to ensure comfort or relieve possible fear of being in small enclosed spaces (claustrophobia). Our previous experience scanning subjects using these methods with similar MRI protocols suggests that rates of withdrawal from MRI procedures due to anxiety or discomfort are extremely low. Given the potential risk for people with metal or magnetic implants, careful screening will be carried out both at the time of initial eligibility screening and again at the MRI appointment. Subjects are prompted to remove any metal objects they may be wearing or have in their clothing prior to scan. If there is any reason to believe that there is a possibility of metal in a subject's body, the subject would need to have an x-ray before having the MRI to confirm that the MRI procedure will be safe for the subject. The subject would only have the fMRI scan if the x-ray showed no metal fragments. The exposure for this x-ray is about the same as a routine chest x-ray. This is a very small amount of radiation and it is unlikely to have any harmful effects. Nevertheless, the subject can choose not

to have the x-ray and not participate in the study protocol.
Incidental Positive Pregnancy Tests- All female subjects will be provided a pregnancy test kit and asked to complete a urinary pregnancy test. Subjects will be informed their tests results will remain confidential. Study personnel will confirm all pregnancy tests and subjects receive their results immediately. Any individual with a positive pregnancy test will no longer be eligible for this study and will not be scanned.
Incidental MRI Findings- Scans will be read by a neuroradiologist for incidental findings. In the case that an MRI technician or other member of the research team suspect that an MRI scan suggests evidence of a significant lesion, Dr. Ragy Girgis (Director of COPE) or Dr. Lawrence Kegeles (study PI) will be notified immediately. If the reading yields a finding of immediate clinical concern, the radiologist will provide an oral report followed by a written note to Dr. Ragy Girgis or Dr. Lawrence Kegeles. Results of the MRI will be provided to the subjects by a study physician. Subjects requesting a letter will receive one using the language provided by the IRB. Please note: All individuals who appear distressed will also be referred to clinical staff at NYSPI, Dr. Ragy Girgis [646-774-5553] or Dr. Lawrence Kegeles [646-774-5560], to further discuss any anxiety or distress. Participants who express any anxiety or distress will be offered the chance to immediately speak with Dr. Girgis or Dr. Kegeles at completion of the interview, and telephone numbers will be provided to contact Dr. Girgis or Dr. Kegeles on the IRB Consent Form that the participant will be given a copy of at completion of the interview.
4. Treatment with Risperidone
We will be vigilant for all side effects, EPS and otherwise and will treat them promptly and appropriately if they occur. If subjects do experience EPS, akathisia or acute dystonia, this would be managed clinically, as follows. For EPS or dystonia, subjects would be given benztropine (Cogentin 1-2 mg/d). For severe akathisia subjects would be given lorazepam (Ativan 0.5 mg/d). In the case of Ativan, although it is likely to improve akathisia, it may itself leave the subject with some sedation or sleepiness, dizziness and unsteadiness. In the case of Cogentin, although it is very likely to rapidly relieve dystonia or EPS, it may itself leave the subject with some sedation or sleepiness, dry mouth or slightly blurred vision. Patients with clinically significant tardive dyskinesia will not be included in this study. Patients who have had a history of NMS from risperidone will not be included in this study. Patients with risk factors that increase the chance of seizures will not be included in the study. For the potential metabolic risks of receiving risperidone, these risks will be discussed with all patients. All patients will also receive full medical screening at baseline. Laboratory abnormalities will be followed as clinically indicated.. In addition, as part of this protocol, patients are made aware that they may discontinue treatment with risperidone and switch to another medication if it is clinically indicated, including for both efficacy and safety reasons.
COVID-related Risks:
Travel: We will instruct subjects to wear a mask in public and while traveling, practice hand hygiene, and stay at least 6 feet away from others. We will tell subjects that if they do not feel comfortable traveling to the medical center for an appointment, for example if the subway or bus they would normally take is crowded, they can reschedule, or we may be able to arrange alternative transportation (if it is the case that alternative transportation, such as Uber or Lyft, can be offered). We will minimize onsite visits to lessen this risk. We will keep our subjects informed about current public health recommendations, such as federal and local government guidelines and directives.
MRI: Risk of exposure in the MRI will be minimized by the COVID safety policies and procedures of the MRI Unit, https://nyspi.org/Covid19MRI.

## Methods to Protect Confidentiality

Describe methods to protect confidentiality
Confidentiality of all participants will be preserved by coding all datasheets and other data sources and maintaining them in locked files. ID numbers will be determined by order of participant entry into the study and will not be related in any way to participant identifying data (i.e., the first participant who is recruited into the study will be subject #1, etc.). Data will be entered into a computerized database. The database is on a computer, which requires a password to access the data. Participants will not be identified by name, only by ID number. All records of the participating subjects will be kept in a locked room with access provided only to staff members. Public dissemination of the results of this research will be reported on subjects collectively and will contain no identifying information about individual participants. Brain imaging data from this study shared with GE (General Electric, the MRI scanner manufacturer) or our colleague at Columbia Biomedical Engineering, Dr. C. Juchem, for evaluation of scanner data quality, will be de-identified raw MRI/MRS data only.

Subjects' MRIs will be interpreted and the results will be shared with them or a physician whom they may designate. Their MRI report will be maintained as part of the database at the Columbia University MRI Research Center if conducted at the Neurological Institute. Their MRI report will be maintained as part of the database at NYS Psychiatric Institute if conducted at the NYS Psychiatric Institute. Any psychiatric diagnoses of potential subjects will not be a part of this report. The link to research subjects' personal information will be kept for 7 years after the research is completed, after which time the link will be destroyed by research staff and the data will become anonymous. The data will be kept in this anonymous form indefinitely. Procedures to ensure confidentiality follow the regulations and policies of all relevant study sites.

As described in the personnel section of the PSF, Dr. Dikoma Shungu at Weill Cornell is a member of the research team and will have access to identifying information only as necessary.

When done remotely, we will use Redcap to obtain consent on the CFs and HIPAA forms. When sending electronic messages to subjects, we will only use NYSPI encrypted email and when sending attachments with PHI we will only use the NYSPI secure file transfer website (https://attach.nyspi.org/) or encrypted NYSPI email or Redcap. When staff work from home, we will use the NYSPI Onedrive Sharepoint system for storing documents or HIPAA compliant storage devices for paper documents. When conducting remote visits, we will use telephone or HIPAA compliant video conferencing.

*Data Sharing*

A data repository has been created by the National Institute of Mental Health (the funding agency for this study) that allows sharing of research data and scientific collaboration. The data repository is accessible only to qualified investigators. All subject data will be de-identified (subjects' names will not be used) and each subject will have a separate identifier called a Global Unique Identifier (GUID) to remove any possibility that the data can be linked directly to them. The GUID is a universal subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). All subjects in this study will be assigned a GUID. The following information will be collected and entered into the study database to generate a GUID: First name, Last name, Middle name (if applicable),

Month of birth, Day of birth, Year of birth, Physical sex at birth, and Name of city/municipality of birth. Once the GUID is generated, all personal information will be deleted from the study database.

During and after the study, the researchers will send deidentified information about subjects' health and behavior to NDCT (National Database for Clinical Trials), which is a national database for information from clinical trials that are sponsored by the government/NIMH. Other researchers nationwide can then file an application with the NIMH to obtain access to deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to privacy.

Subjects may decide now or later that they do not want to share their information using NDCT. If so, they may contact the researchers conducting this study, and they will tell NDCT, which can stop sharing the research information. However, NDCT cannot take back information that was shared before subjects change their minds.

*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
The potential direct benefits of risperidone treatment are that the subjects are likely to experience an improvement in symptoms. Participants will also receive medical and psychiatric assessments by skilled, experienced clinicians.

There are no direct benefits associated with participating in the MRI portion of this study.

## 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 $100 per MRI scan (up to 2 scans). In addition, they will receive $50 per session (includes up to 3 screening/baseline sessions and weekly sessions; maximum of $550) for additional clinical, screening and neuropsychological assessments that they do outside of the MRI machine. If subjects agree to come in as a standby subject, they will receive a check for $50. If they come in as a standby subject and are asked to participate in the scanning procedures, they will be paid according to the protocol. If they come in as a standby subject multiple times, they will be paid $50 for each visit. The money will be sent by check to their home address and they can expect to receive it within 2-3 weeks of the study day, or they will

be paid in cash **or via Paypal.** We will also reimburse for local transportation.

## References

References
Abi-Dargham A, Gil R, Krystal J, Baldwin R, Seibyl J, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M: Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. Am J Psychiatry 1998; 155: 761–767.

Boonstra, N., et al., Duration of untreated psychosis and negative symptoms--a systematic review and metaanalysis of individual patient data. Schizophr Res, 2012. 142(1-3): 12-19.

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D: Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proceedings of the National Academy of Sciences of the United States of America 1997; 94: 2569-2574.

Breier A, Adler CM, Weisenfeld N, Su TP, Elman I, Picken L, Malhotra AK, Pickar D: Effects of NMDA antagonism on striatal dopamine release in healthy subjects: Application of a novel PET approach. Synapse 1998; 29: 142–147.

Carlsson A: Interactions between monoamines, Glutamate, and GABA In Schizophrenia: New Evidence. Annual Rev Pharmacol Toxicol 2001; 41: 237-260.

Carlsson A, Lindqvist M: Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol 1963; 20: 140–144.

Coyle JT: The glutamatergic dysfunction hypothesis for schizophrenia. Harvard Rev Psychiatr 1996; 3: 241-253.

Davis KL, Kahn RS, Ko G, Davidson M: Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 1991; 148: 1474-1486.

Farooq, S., et al., The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. Schizophr Res, 2009. 109(1-3): p. 15-23

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 2012; 69(3):220-229.

Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The Psychosis High-Risk State A Comprehensive State-of-the-Art Review. JAMA psychiatry Jan 2013;70(1):107-120.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86:1119-27.

Hollingshead, A. A. (1975). Four-factor index of social status. Unpublished manuscript, Yale University, New Haven, CT.

Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatr 1991; 148: 1301-1308.

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

Lodge DJ, Grace AA: Aberrant Hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. J Neurosci 2007; 27(42):11424-11430.

Laruelle M, Abi-Dargham A: Dopamine as the wind of the psychotic fire: New evidence from brain imaging studies. J Psychopharmacol 1999; 13: 358-371.

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, De Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB: Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug free schizophrenic subjects. Proc Natl Acad Sci 1996; 93: 9235-9240.

Moghaddam B, Adams B, Verma A, Daly D: Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997; 17(8): 2921-2927.

Olney JW, Farber NB: Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995; 52: 998-1007.

Olsen KA, Rosenbaum B. Prospective investigations of the prodromal state of schizophrenia: review of studies. Acta Psychiat Scand Apr 2006;113(4):247-272.

Perkins, D.O., et al., Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry, 2005. 162(10): 1785-804.

Snyder SH: The dopamine hypothesis of schizophrenia: Focus on dopamine receptor. Am J Psychiatry 1976;133: 197-202.

Tamminga CA: Schizophrenia and glutamatergic transmission. Crit Rev Neurobiol 1998; 12: 21-36.

Tamminga CA, Holcomb HH, Gao XM, Lahti AC: Glutamate pharmacology and the treatment of schizophrenia: Current status and future directions. Int Clin Psychopharmacol 1995; 3: 29-37.

Yung AR, Yuen HP, Berger G, Francey S, Hung TC, et al: Declining transition rate in ultra-high risk (prodromal) services: dilution or reduction of risk? Schizophr Bull 2007; 33:673–81.

## Uploads

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## Statistical Analysis Plan

Sections from “Research strategy”

### Power Analysis

**Aims 1 & 2 – Glu and GABA Differences:** In our 6 pilot MRS studies described in Section **D1.1**, we found significant group mean GABA and Glu differences in the MPFC and/or DCA with effect sizes greater than 0.9. This would yield power >0.9 to detect the hypothesized elevations of these measures at the $\alpha$ = 0.05 level (2-tailed) with the proposed sample size of 60 FEMN and matched controls. The present studies thus have more than adequate power to detect the postulated neurotransmitter differences at all the measurement time points.

**Aim 3 – Clinical Correlations.** With 25 FEMN subjects or less we found preliminary GABA and Glu vs. PANSS correlations that did not survive Bonferroni correction. With 60 FEMN subjects, correlations with Pearson coefficient as low as 0.35 will be detected at $\alpha$ = 0.05 with 80% power.

### Statistical Analyses and Hypothesis Testing

**(a)** ***MPFC and DCA GABA and Glu levels in FEMN at baseline and on follow-up:*** The follow-up period is defined as the 4-week treatment period for the FEMN group. For our primary analyses, linear mixed-effects models for each region of interest (MPFC, DCA) with group (FEP, HC) and MRS outcome measures (GABA and Glu) as fixed effects, will be used for omnibus testing. Baseline and follow-up MRS outcome measures will be repeated measures in the models. Effects on the outcome measures of gender, ethnicity, will be assessed by ANCOVA, using these factors as covariates in the mixed-effects models and accepting the most parsimonious covariates according to the Akaike information criterion (Sakamoto et al 1986). Significant results from the omnibus testing will be followed with post hoc two tailed independent samples Student’s t-tests of the group differences in the baseline, follow-up and follow-up **change** values of the MRS outcome measures.

**(b) Clinical Correlations:** We will use the Pearson product moment coefficient to test for postulated relationships among clinical symptoms (PANSS), treatment response and the MRS outcome measures. Effects of covariates will be addressed with ANCOVA as above.

**(d) Missing Data**: Maximum likelihood (ML), as implemented robustly in the MPlus 7 software package (Muthén & Muthén 1998-2012) will be used to deal with any missing data in our regression models. ML is relatively simple, has a high algorithmic efficiency and enables incorporation of covariates as auxiliary variables, to allow accuracy and power to be maximized in the analysis of data sets with missing values (Enders 2010).