Protocol Title:
Pet Imaging Study of Old-Order Amish Patients with CNTNAP2 Mutations

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Cover Sheet

Choose from the following that is applicable to your study
I am proposing an amendment only to an existing protocol

Division & Personnel

Division

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

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Dr. Kevin Strauss at the Clinic for Special Children at 535 Bunker Hill Road in Strasburg, PA (in close

proximity to Lancaster, PA)

Amendment

Describe the change(s) being made
I am uploading our new, revised HIPAA form (we forgot to revise this for our recent amendment that was submitted and subsequently approved earlier this week). As previously discussed, we were amending our PSF and CF to now clearly state that the study is currently not funding by the NIMH but rather by a philanthropic donation that was made to us to complete this study. As such, our HIPAA form had to be revised to clearly state this as well.
Provide the rationale for the change(s)
See description above.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
This amendment will not affect risks/benefits for study subjects in any way.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
CFs were already modified earlier this week and were approved by the IRB.

Procedures

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

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Studies of DNA
✓ PET/SPECT Scan
✓ MRI
✓ Arterial Line
✓ Use of Investigational Drug or Device

Population

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

✓ Adults who may have impaired decision-making ability
✓ Adults
✓ Individuals with Psychosis

Research Support/Funding

Will an existing internal account be used to support the project?
Yes

Describe internal account
Financial resources made available as a gift from a donor for this specific project. Will provide details of internal account as soon as possible (when funds are transferred).
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
Other
Sponsor
N/A
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
The Trustees of Columbia University in the City of New York

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)..
Clinic for Special Children at 535 Bunker Hill Road in Strasburg, PA

Lay Summary of Proposed Research

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Current treatments for psychotic disorders such as schizophrenia (SCZ) have major shortcomings, including having only limited effectiveness while often causing severe and treatment-limiting side effects. As such, there is a desperate need for a new class of psychotropic medications that target disease mechanisms rather than solely targeting symptomatology. Furthermore, a significant limitation of current treatment approaches is that they primarily target symptom categories, rather than clinical dimensions of psychopathology, which may be more proximal to the underlying disease mechanisms, and thus more amenable to specific neurobiological intervention. The present project is being performed under the FAST-Fail approach to develop novel intervention strategies for psychosis disorders.

The present project derives from studies showing that a recently characterized genetic mutation of the CNTNAP2 (Contactin-associated protein-like 2) gene that is present in the Old-Order Amish Founder population dramatically increases risk for SCZ and other disorders with prominent social/cognitive impairment such as autism spectrum disorder (ASD) or specific language impairment (SLI; 1, 2). Furthermore, it has recently been shown, that in animal models, this mutation leads to significant downstream dysregulation of the mechanistic target of rapamycin (mTOR) signaling pathway and dysregulation of glutamatergic neurotransmission, leading to hyperexpression of metabotropic glutamate 5 receptors (mGluR5) in the frontal cortex and other brain regions. In rodents, this disease phenotype can be reversed by selective mTOR kinase inhibitors (3), suggesting a potential novel intervention strategy not only for identified CNTNAP2 mutation carriers, but also for other patients with phenotypically similar symptom constellations across diagnostic boundaries.

Although the mTOR kinase target is well-validated based upon preclinical models, at present there are no biomarkers available to directly assay mTOR kinase activity in the brain, preventing direct assessment of target engagement. Instead, this project proposes to use PET-determined mGluR5 expression as a surrogate measure for level of activity of the mTOR kinase pathway. Objective alterations in tissue expression of mGluR5 have been demonstrated in individuals homozygous for the CNTNAP2 mutation, suggesting that mGluR5 expression may be altered in heterozygotes as well, and that levels of alteration will be sufficiently detectable with mGluR5 PET binding. Furthermore, well-validated ligands are available for the mGluR5 site, permitting assessment of mGluR5 binding as a potential target engagement biomarker.

The primary goal of the present study is to evaluate the utility of mGluR5 binding as measured by PET as a biomarker of the CNTNAP2 mutation and related /mTOR kinase pathway dysregulation. If successful, the present project will validate PET mGluR5 binding as a functional target engagement marker for future proof-of-concept (POC) studies targeting the mTOR kinase pathway. The long-term goal of this line of research is the evaluation of mammalian target of rapamycin (mTOR) kinase inhibitors that directly target the molecular pathways affected by CNTNAP2 mutations, as a treatment for Research Domain Criteria (RDoC)-relevant subgroups of psychosis-spectrum populations. Several well-tolerated, high affinity mTOR kinase inhibitors are presently in late-stage clinical development for indications such as brain tumor but might, at lower dose, be effective treatments for mTOR-kinase hyperactivity associated with neuropsychiatric illness. At present, however, clinical trials with such agents in neuropsychiatric disorders are limited by the lack of target engagement biomarkers that could be used to guide “FAST-Fail”-type mechanistic studies. The goal of the present study is the development of a biomarker –PET mGluR5 binding

– that can be used as a target engagement biomarker to guide future intervention studies.

Background, Significance and Rationale

Background, Significance and Rationale
Background:

SCZ and other psychosis-spectrum disorders are etiologically heterogeneous with complex genetic architecture. One identified risk gene for SCZ is the CNTNAP2 (also known as CASPR2) gene. Mutations of this gene lead to a phenotype that is diagnosed alternately as SCZ, ASD, or SLI and is associated with severe impairments in social cognition (2). A specific mutation of this gene is highly prevalent in the Old-Order Amish Founder population and leads to severe psychophysiological disturbance in affected individuals (4).

In mice, deletion of the Cntnap2 gene leads to hyperactivation of signaling via the mTOR pathway, and overexpression of mGluR5 and other neurotransmitter receptors, along with neurophysiological and behavioral dysfunction (3). mTOR kinase inhibitors, such as the compounds WYE125132 and AZD2014, reverse both the neurophysiological and behavioral deficits associated with Cntnap2 deletion, as well as the overexpression of mGluR5 receptors. In Old-Order Amish individuals with the CNTNAP2 mutation, a highly significant upregulation of mGluR5 expression is observed in post-surgical cortical tissue from patients who underwent surgical excision for treatment of epilepsy suggesting that the mouse model significantly recapitulates the disease phenotype. If so, this finding suggests that mTOR kinase inhibitors may play a unique role in the treatment of psychosis-spectrum patients with genotypic disturbances that converge on CNTNAP2 signaling or mTOR over activation.

In this mGluR5 CNTNAP2 Amish/**Mennonite** study, we will focus on mGluR5 PET binding as a surrogate measure for level of activity of the mTOR kinase pathway. This study is being conducted by the New York State Psychiatric Institute (NYSPI) and the Research Foundation for Mental Hygiene, Inc. (RFMH) and will take place at Columbia University Medical Center (CUMC) in New York City and at our research office in Strasburg, Pennsylvania. Of note, given that this study is being conducted by NYSPI, all NYSPI policies will be followed. Subjects (n=20) with the CNTNAP2 mutation with SCZ or a related condition will be recruited from the Amish **and Mennonite** community and brought to CUMC for detailed investigation. Affected individuals will be compared to Amish **or Mennonite** control patients drawn from the same families but not harboring CNTNAP2 mutations (n=20). The primary measure will consist of mGluR5 PET binding in DLPFC. In addition, secondary analyses will assess binding in other brain regions such as hippocampus and visual cortex. Exploratory measures, as well as relationships between PET mGluR5 binding and clinical symptomatology, will be assessed.

Clinical diagnosis: Among Amish **and Mennonite** individuals who are heterozygous or homozygous for the CNTNAP2 mutation, a clinical phenotype is observed that incorporates disturbances in social cognition and language function, as well as psychosis. For the current study, in order to select for a phenotypically homogenous cohort of patients, we will recruit 20 subjects who meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for psychotic disorder, including schizophrenia. Because we anticipate a strong comorbidity with developmental disorders, such as ASD, diagnostic criteria

for psychosis will be made if subjects meet criterion A (i.e., hallucinations, delusions, disorganization) for schizophrenia without regard to co-morbid diagnoses.

We will be using [18F]FPEB for the current investigation of mGluR5 PET binding in the Amish and **Mennonite** patients with CNTNAP2 mutations. The tracer will be produced on site at the Kreitchman center at CUMC. In addition to the primary measures, secondary measures will include measures of positive and negative symptoms and will be incorporated to assess mechanisms mediating between impaired mTOR kinase function and the clinical symptomatology of psychotic spectrum disorders.

Significance:

The primary goal of the present protocol is to demonstrate that PET mGluR5 binding is sensitive to the increases in mGluR5 expression that have been demonstrated in surgically excised brain tissue obtained from CNTNAP2 mutation carriers (as well as in brains of Cntnap2 mutant mice), and to detect additional biomarkers that may be useful for establishing target engagement in future clinical trials.

This present study will verify that the increase in mGluR5 expression that is detected ex vivo can also be detected in vivo using PET mGluR5 markers. If successful, this will provide a biomarker that will enable future POC studies targeting mTOR or other CNTNAP2-related signaling pathways as potential novel treatments for psychotic disorders. More generally, this project represents one of the first biomarker studies for patients who harbor a specific mutation in an important SCZ candidate gene and could lead the way to the first mutation-specific clinical trial in psychiatry. As such, it has the potential to shift paradigms in terms of clinical assessment and treatment. The present study will illustrate the major clinical benefit of identifying specific subpopulations that suffer from schizophrenia, which can benefit from a treatment that targets disease mechanism and will pave the way for similar personalized medicine trials in other patient populations who carry specific genetic risk factors.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Primary Aims:

The overall objective of this line of investigation is to develop mTOR kinase inhibitors as novel treatments for psychosis disorders. The primary aim of this study is to validate PET mGluR5 binding as a downstream marker of mTOR kinase hyperactivity, using individuals with CNTNAP2 as an “experiment of nature” to assess consequences of mTOR kinase-pathway mutations on PET mGluR5 binding. Our primary hypothesis is that PET mGluR5 binding will be altered in DLPFC of CNTNAP2 mutation carriers vs. first- or second degree relatives without the mutation. If confirmed, this will support use of PET mGluR5 binding as target engagement biomarkers for future interventional type studies.

Secondary Aims:

Although primary analyses will focus on DLPFC based on preclinical data, secondary analyses will evaluate PET mGluR5 binding in other brain regions of potential relevance, including hippocampus (HIPP) and

primary visual cortex (occipital pole) in order to determine ideal regions of interest for future intervention studies.

Exploratory Aims:

Exploratory aims include determining the interrelationship between PET mGluR5 binding across brain regions and both symptoms and neurocognitive function in psychosis disorder patients.

Description of Subject Population

Sample #1

Specify subject population
patients
Number of completers required to accomplish study aims
20
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
18-59

Sample #2

Specify subject population
controls
Number of completers required to accomplish study aims
20
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
18-59

Gender, Racial and Ethnic Breakdown
Because of the unique features of this population, inclusion of more general research subjects is not feasible. Furthermore, because the target population consists of white, non-Hispanic individuals, inclusion of non-white and of Hispanic individuals is not feasible. Male and female subjects will be recruited equally.
Description of subject population
This study will exclusively recruit patients from the Amish and Mennonite community in Lancaster, PA. All subjects have been previously identified and were screened for the CNTNAP2 mutation prior to enrollment. This represents a unique population that we expect will be specifically informative regarding the pathophysiology of schizophrenia.

Recruitment Procedures

Describe settings where recruitment will occur

Study subjects will be recruited from the Amish and Menonite community in Lancaster, PA as well as other areas where subjects from this community reside (e.g., Upstate New York). All subjects will have been screened for the CNTNAP2 mutation prior to inclusion in the study by clinical researchers at the Clinic for Special Children in Strasburg, Pennsylvania under an IRB-approved protocol at that clinic that provides them with permission to re-contact subjects. The researchers at this clinic have put together a list of potentially eligible subjects for this study from the Amish and Mennonite community who are followed at the Clinic for Special Children and who are known to carry the CNTNAP2 mutation. All subjects have a chart diagnosis, and the clinicians from the Clinic for Special Children will refer patients with a history of psychotic symptoms who are potentially interested in participating in our study to our research clinic in Strasburg, PA.

How and by whom will subjects be approached and/or recruited?
All patients are currently receiving clinical care at the Clinic for Special Children. As such, we will ensure that Dr. Strauss will obtain a record of permission from individuals prior to the research coordinator contacting the participants.

We are planning to recruit 20 subjects with a psychotic spectrum disorder and for each of these subjects, an unaffected 1st- or 2nd degree relative (i.e., a total of 20 unaffected subjects). We will ensure that the proband will first get signed permission prior to our team reaching out to the unaffected relatives.

After Dr. Strauss from the Clinic for Special Children obtains record of permission from individuals prior to our research coordinating contacting the participants, we will meet with patients at our research office and we will explain the purpose of the study. We will obtain consent from patients for participation in our study and will subsequently carry out the Structured Clinical Interview for DSM-5 (SCID) interview to determine whether they meet criteria for SCZ or PDNEC. Of note, both the patients who are known to carry the CNTNAP2 mutation as well as their 1st- and 2nd degree relatives who do not carry the CNTNAP2 mutation will undergo a clinical assessment for psychotic spectrum disorders as well as any other related psychiatric illness, using the Structured Clinical Interview for DSM Disorders – V (SCID-V).

We will hire a full time study coordinator who is an active member of the Amish community and based in Strasburg, PA and who will work closely with local researchers. She/he will have access to records and permission to contact individuals based on prior IRB approvals giving permission to re-contact. Dr. Markx will maintain weekly contact with the M.D. and the study coordinator in Strasburg, and will visit biweekly in person to review recruitment progress and procedures.

How will the study be advertised/publicized?
Not applicable, recruitment is referral based.
Do you have ads/recruitment material requiring review at this time?

No
Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
patients
Create or insert table to describe the inclusion criteria and methods to ascertain them
1. Meets DMS-5 diagnostic criteria for psychotic disorder, including SCZ/schizoaffective disorder (SAD) or psychotic disorder not elsewhere classified (PDNEC) -- Ascertained by history and SCID interview

2. Aged 18-59 years -- Ascertained by history

3. Genetic confirmation that patient carries CNTNAP2 mutation -- Ascertained by genetic testing

4. All patients will be of Amish and/or Mennonite descent -- Ascertained by history

5. A relative will be willing to be part of the study and this relative will travel with the participant to CUMC in New York City and back to Strasburg, PA -- Ascertained by history

6. In the judgment of the participant's treating physician as well as the evaluating consenter, the patient is stable enough to travel and participate in the study

Of note, all subjects have already undergone genetic testing for the CNTNAP2 mutation by Dr. Kevin Strauss (who is a consultant on this study) at the Clinic for Special Children (CSC). We will therefore be able to recruit patients who are known to carry the CNTNAP2 mutation through referrals from the CSC. We are not collecting DNA and will not story any genetic samples in the NIH repository for this study.

For visit 1, our office will be located in Strasburg, PA (135 E Main street, Strasburg, PA 17570, Phone: 717-687-6362), which is in close proximity to Lancaster, PA.
Some of the subjects live in isolated, rural areas of Pennsylvania that are not in close proximity to our Strasburg office. Therefore, subjects will be first consented in one of two possible locations: 1) Our research clinic in Strasburg, Pennsylvania or 2) In the patient's home (depending on what is more convenient/preferable for the subject). Consent will be obtained by approved NYSPI personnel. Capacity will be assessed at either location by Drs. Kevin Strauss, Holmes Morten, or Katie Williams (all of whom work at the Clinic for Special Children in Strasburg, PA, which specializes in working with Amish and Mennonite patient populations).

Key aspects of the consent process are 1) the protocol will be conducted under supervision of the NYSPI IRB, 2) consent will be obtained by approved NYSI personnel, 3) capacity for consent will be assessed by treating physicians unassociated with the research team, who will also certify that participation of the subject is appropriate in research is appropriate to his/her condition, and 4) the family will be involved as well in decision to consent. For travel, it will be important to note that travel will be arranged by the study coordinator and patients will travel accompanied by responsible family members. NYSPI personnel will remain in contact with patients until they are back home. For office space, key points are that office space will be under the control of NYSPI and that the same confidentiality policies in place at NYSPI (e.g. HIPAA compliance) will be in place at the rented space as well.

Create or insert table to describe the exclusion criteria and methods to ascertain them
1. Positive urine toxicology for drugs of abuse, including cannabinoids, amphetamine, benzodiazepines, barbiturates, cocaine, methadone, opiates, and phencyclidine -- Ascertained by urine toxicology

2. Positive history of severe neurological illness or history of brain trauma -- Ascertained by history

3. Positive history of severe medical illness that would increase risk due to PET scan procedure, or interfere with interpretation of research findings -- Ascertained by history

4. Low hemoglobin (Hb < 11 g/dL in males, Hb < 10 g/dL in females) -- Ascertained by labs

5. Lifetime exposure to radiation in the workplace, or lifetime history of participation in nuclear medicine procedures, including research protocols (ascertained by history). However, in case of previous exposure to radioactivity due to research studies, subjects will be eligible if all conditions listed below are fulfilled:

The research studies in question have been performed in the context of a protocol from the Division of Translational Imaging (Anissa Abi-Dargham, M.D., Director), or as part of a research study within another division at Columbia University/NYSPI and the injected dose and dosimetry of the radiotracer are known.

Except for research studies, the patient has had no lifetime exposure to radiation in the workplace or in nuclear medicine procedures.

Adding the previous exposure to the exposure due to this study will result in a yearly cumulative exposure lower than the limit defined by the FDA for research subjects

6. Blood donation within 8 weeks of study -- Ascertained by history

7. Presence of clinically significant brain abnormalities -- Ascertained by history

8. For female patients of child-bearing age who are not surgically sterilized and between menarche and 1 year postmenopausal: Must test negative for pregnancy at the time of enrollment and prior to PET scan based on a serum pregnancy test. Woman who are breast-feeding are also excluded. Of note, since Amish and Mennonite patients may not use contraceptive methods, we are taking specific precautions to ensure that women of childbearing age will undergo pregnancy testing at the appropriate times. Specifically, if there are

2 weeks or less between the time of scheduling and the PET scan date in New York, we will ask them not to have unprotected sex until they come to New York. If there are more than 2 weeks between the scheduling and the PET scan date in New York, we will re-screen the subjects with a pregnancy test 2 weeks before their PET scan date in New York and will ask them not to have intercourse until after they complete their PET scan. -- Ascertained by labs (pregnancy test)

9. 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 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. -- Ascertained by history

10. Medicinal patch, unless removed prior to the MR scan -- Ascertained by history

11. Patients: Current treatment with clozapine and/or medications other than antipsychotics/PRN anxiolytics -- Ascertained by history

12. Use of the medications that would interfere with mGluR5 binding, including lamotrigine, gabapentin, topiramate, phenobarbital, pregabalin, zonisamide, N-acetylcysteine, D-cycloserine -- Ascertained by history

Of note, the reason that clozapine is excluded is because it, similar to the medications listed under Exclusion criterion 13, would potentially interfere with mGluR5 binding. However, other antipsychotics are allowed because several studies have not demonstrated that these antipsychotics interfere in any way with mGluR5 binding (--see Matosin N., et al., Metabotropic glutamate receptor 5 binding and protein expression in schizophrenia and following antipsychotic drug treatment. Schizophrenia Research 2013;146: 170-176).

Furthermore, all patients will remain on their medication for the duration of this study. No medications will be discontinued for the purpose of this study.

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
controls
Create or insert table to describe the inclusion criteria and methods to ascertain them
1. Aged 18-59 years -- Ascertained by history
2. Genetic confirmation that subject does not carry CNTNAP2 mutation -- Ascertained by genetic testing
3. First- or second-degree relative of subject of Amish/Mennonite descent with CNTNAP2 mutation --

Ascertained by history
Create or insert table to describe the exclusion criteria and methods to ascertain them
Lifetime history of antipsychotic or antidepressant use -- Ascertained by history

Otherwise, same as for patient group

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
Consent Procedures:

Written informed consent, approved by the institutions' IRBs and the NIMH Data Safety and Monitoring Board (DSMB), will be obtained from each participant prior to entering the study. The informed consent document will explain in simple terms, before the subject is entered into the study, the risks and benefits to the subject. The informed consent document will contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time.

The nature of the procedures and the alternatives to study participation will be discussed with each subject prior to obtaining written informed consent. Subjects will be informed that the information they provide will be kept confidential except within the research team and how that confidentiality will be assured. They will be told that their records are filed by number, not by name, and that all records are kept in locked files accessible only to research personnel. Consent will be obtained after a thorough explanation of the study by the PIs and an opportunity for the participant to ask questions about the study. The consent form will be signed and dated by the subject and PIs.

It will be the responsibility of the PIs to ensure that an informed consent form is obtained from each

participant and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and in accordance with current state and federal regulations. The signed informed consent document will be retained with study records. Each participant will be given a copy of his or her signed informed consent.
Describe Study Consent Procedures
Consent Documents:

The consent form contains all required elements. The consent documents submitted with this protocol, including: patient population and unaffected family member.

In the consent form and in the consent discussion, subjects will be advised fully of the study procedures, the amount of time required of them, the possible risks and benefits, the voluntary nature of their participation, their right to refuse participation without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigators.

Some of the subjects live in isolated, rural areas of Pennsylvania that are not in close proximity to our Strasburg office. Therefore, we are proposing that subjects will be first consented in one of two possible locations: 1) our research clinic in Strasburg, Pennsylvania or 2) in the subject's home, depending on what is more convenient/preferable for the subject. In addition to consenting the subjects, all other screening interviews/assessments, except for the collection of blood and urine samples and the EKG and physical exam, will all take place at both of these locations. However, the collection of blood and urine samples, the EKG exam, and the physical exam will take place exclusively at our Strasburg office.

Subjects will be first consented in 1) our research clinic in Strasburg, Pennsylvania or 2) in the subjects home, depending on hat is more convenient/preferable for the subject. Consenting will be done by Dr. Sander Markx or any of the other consenters listed. Following the assessment in Strasburg or in the patient's home, subjects will be re-consented when they arrive at CUMC. This is to ensure that patients are still able to provide consent for the study since there may be some time between the initial consent in Strasburg and when patients can be scheduled to come to CUMC for the PET and MRI scan.

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

Persons designated to discuss and document consent

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

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment
Capacity will be assessed independently by an independent clinician who is not a member of the research team. These will include Drs. Kevin Strauss, Katie Williams, Holmes Morton, Roberto Gil, Larry Kegeles, Jodi Weinstein, David Kimhy, Seth Berger, Robin Nelson, Holmes Morton and Winnie Leung. Great care will be taken to ensure that the subject is able to give informed consent. This process will involve careful explanation of the consent form by a member of the research staff and questioning to ensure understanding of the procedures and risks of the study.

Dr. Kevin Strauss is the Medical Director of the Clinic for Special Children (CSC) in Lancaster (Strasburg), P.A. Dr. Williams also works as one of the attendings at the CSC. Drs. Strauss and Williams both specialize in working with Amish and Mennonite patient populations but are both independent of our the propose study and are therefore able to assist in the independent assessment of capacity at our Strasburg clinic site or in the patients' homes.

Dr. Holmes Morton is the founder of the Clinic for Special Children (CSC) and currently works as an attending physician at the CSC. Like Dr. Strauss, Dr. Holmes specializes in working with Amish and Mennonite patient populations. Given that he is the treating physician who is unassociated with the research team, he will be able to assist in the capacity assessment at either the Strasburg (Lancaster) site or in the patients' homes.

Study Procedures

Describe the procedures required for this study
We will obtain consent from patients for participation in our study and will subsequently carry out the Structured Clinical Interview for DSM-5 (SCID) interview to determine whether they meet criteria for SCZ or PDNEC.

After providing informed consent, subjects will undergo a 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, thyroid tests, electrocardiogram [EKG]) and psychiatric screening (i.e., SCID, Columbia Suicide Severity Rating Scale [CSSRS]) to confirm eligibility.

Of note, the genetic testing for the CNTNAP2 mutation has already taken place by Dr. Kevin Strauss (who is a consultant on this study) at the Clinic for Special Children. We will therefore be able to recruit patients who are known to carry the CNTNAP2 mutation.

For visit 1, our office will be located in Strasburg, PA (135 E Main street, Strasburg, PA 17570, Phone: 717-687-6362), which is in close proximity to the CSC as well as close to Lancaster, PA.
Some of the subjects live in isolated, rural areas of Pennsylvania that are not in close proximity to our Strasburg office. Therefore, subjects will be first consented in one of two possible locations: 1) Our research clinic in Strasburg, Pennsylvania or 2) In the patient's home (depending on what is more convenient/preferable for the subject). Consent will be obtained by approved NYSPI personnel. Capacity will be assessed at either location by Drs. Kevin Strauss, Holmes Morton, or Katie Williams (all of whom work at the Clinic for Special Children in Strasburg, PA, which specializes in working with Amish and Mennonite patient populations).

Key aspects of the consent process are 1) the protocol will be conducted under supervision of the NYSPI IRB, 2) consent will be obtained by approved NYSPI personnel, 3) capacity for consent will be assessed by treating physicians unassociated with the research team, who will also certify that participation of the subject is appropriate in research is appropriate to his/her condition, and 4) the family will be involved as well in decision to consent. For travel, it will be important to note that travel will be arranged by the study coordinator and patients will travel accompanied by responsible family members. NYSPI personnel will remain in contact with patients until they are back home. For office space, key points are that office space will be under the control of NYSPI and that the same confidentiality policies in place at NYSPI (e.g., HIPAA compliance) will be in place at the rented space as well.

Of note, Dr. Markx will not be providing clinical care in Pennsylvania, so that he does not require medical license in that state. When patients are at CUMC, their care will be coordinated by the study MDs who will have full clinical responsibility until the patients return to Pennsylvania.

Once scheduling has occurred, subjects will be transported to NYSPI/CUMC, where they will spend 2-3 days for further assessments. These will include whole-brain mGluR5 PET binding, a structural MRI for PET co-registration, and behavioral measures, including Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and CSSRS.

The CSSRS will be performed in Strasburg, PA during the Screening/Evaluation (Visit 1) and at CUMC on Day 2, and results will be reviewed by a board-certified psychiatrist.

We will also perform the Clinical Global Impression (CGI-S) assessment during the Screening/Evaluation (Visit 1) and at Columbia/RFMH on Day 2, and results will be reviewed by a board-certified psychiatrist.

PET scan:

PET experiments will be conducted with the mCT scanner in the PET Suite on the R1 level of the Public Health Building of CUMC.

Subject preparation

Subjects participating in the study will be escorted on PET scan day by a research staff member to the R1 level of the Public Health Building of CUMC where the PET scanner is located. A research staff person will stay with the subject throughout the procedure. A serum pregnancy test is performed on female subjects to confirm that pregnancy has not occurred between the time of the screening and the PET. The preparation of the subject will include the placement of an arterial and a venous catheter.

The purposes of these lines are as follows:

- Venous catheter: [18F]FPEB injection (single bolus)
- Arterial catheter: - blood sampling for [18F]FPEB arterial concentration

The arterial catheter will be placed after completion of the Allen test and infiltration of the skin with 1 to 2% lidocaine. The radiochemistry laboratory and PET suite staff will be in frequent communication regarding the status of preparation of the research subject (such as placement of venous line) and the progress of the radiotracer synthesis. As scan time approaches, the subject will be placed in a supine position on the camera table and will have vital signs (blood pressure and heart rate) obtained. Head will be positioned and a headholder will be used to decrease head movement during the scan. A low dose CT attenuation scan is then obtained prior [18F]FPEB administration. At the end of the attenuation scan, 5 mCi or less of [18F]FPEB will be injected intravenously. The dose of [18F]FPEB, diluted in a 10 cc syringe, will be given as a single bolus over a period of up to 30 seconds. [18F]FPEB will be prepared by the central radio-ligand staff of the PET Center and will be administered by an approved Nuclear Medicine physician. For this study, authorized Nuclear Medicine physicians are Randy Yeh, M.D. and Arif Sheikh, M.D.

Study physicians will be present for all radiotracer injections. All study physicians have New York State Medical license and have had extensive training and experience with these types of PET studies. [18F]FPEB will be synthesized and tested for purity and sterility according to our standard procedure. The injected dose of [18F]FPEB for each [18F]FPEB scan will not exceed 5 mCi. Total scan time will be 90 minutes.

Emission scan protocol

The emission scan will be started at the time of injection of [18F]FPEB. Following the injection, scan data will be acquired for 90 minutes. During the scan, blood samples (up to 150 ml per scan) will be drawn through the arterial line for determination of [18F]FPEB and arterial concentration at regular intervals. The study physician or Nuclear Medicine physician will evaluate the reconstructed PET image in order to ensure tracer uptake in the brain and will inform the radiochemist if there is a lack of expected uptake in the brain. All subjects will be monitored by the study physician at the time of injection and a study physician or nurse will be present in the PET suite while the a-line is in place.

At the completion of the scan the catheters will be removed (a-line by a physician), and the subject will be evaluated (including mental status and vital signs) by a study physician. Vital signs, and

physical exam will be performed prior to discharge from the PET suite.

Data Analysis

PET data will be reconstructed into images using the appropriate reconstruction protocols and filters. PET images will be co-registered to the MRI and regional time activity curves will be measured. Data will be fitted to pharmacokinetic models, and relevant pharmacokinetic parameters, including the percent of receptors engaged by dopamine, will be estimated based on the model fitting procedures.

MRI Scan:

Structural MRI will be obtained to permit co-registration of PET images. For structural MRI, T1-weighted high resolution anatomical scans will be acquired on a 3 T GE scanner in coronal planes orthogonal to the AC-PC line, producing 142 1.5-mm slices. Total scan time will be 30 min.

Behavioral Measurements:

Psychosis symptoms will be assessed using the PANSS. In addition, the CGI-S scale will be used to assess global function, and the CSSRS will be used to verify absence of suicidal ideation.

The PANNS is a clinical interview used for measuring symptom severity of patients, which usually takes approximately 20-30 minutes to conduct. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers.

The CGI-S rating scale is a commonly used measure of symptom severity, in treatment studies of patients with mental disorders. The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

The CSSRS is a screening tool, which has demonstrated ability to reliably measure suicidal ideation and behavior in suicidal and non-suicidal individuals.

Subjects will be spending 2 nights in a hotel in close proximity to NYSPI/CUMC. If a subject specifically requests it or if the study M.D. deems it clinically necessary, subjects can also stay overnight at the Adult Inpatient Unit at the Irving Institute for Clinical and Translational Research at CUMC. The Principal Investigator and several unaffected/healthy family members will accompany the patients during their travel and the unaffected family members will be staying with the participants throughout their visit – both at the hotel as well as the inpatient unit where there is an option for family members to stay overnight as well. The participants will all receive $650 – this includes time and effort for 2 days of testing as well as the overnight stay.

Subjects will be staying at one of following hotels:

- Hotel Newton 2528 Broadway at West 96th Street New York, NY 10025

- Hotel Beacon NYC 2130 Broadway at 75th Street New York, NY 10023
- Hotel Belleclaire 250 W. 77th Street New York, NY 10024
- The Lucerne 201 West 79th Street at Amsterdam Avenue New York, NY 10024

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
A patient will be discontinued from the study 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) Significant distress/discomfort.
(4) CGI-S score of 6 or 7

A safety plan will be discussed both with the patient as well as the relative in the event that the patient deteriorates at any point during the trip.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
After providing informed consent, subjects will undergo a 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, thyroid tests, electrocardiogram [EKG]) and psychiatric screening (i.e., SCID, Columbia Suicide Severity Rating Scale [CSSRS]) to confirm eligibility.

Vulnerable populations will be excluded from this study, including pregnant women. In order to identify women who are pregnant, all women of childbearing potential will undergo a blood pregnancy test both at the time of enrollment and prior to PET scanning.

Venous blood sampling in the amount of 15 mL for screening laboratory tests and an additional 150 mL for metabolite analysis of [18F]FPEB will be obtained for this study. This volume of blood is not expected to have any serious negative effects on the study participants. Adverse effects of blood sampling will be minimized by exclusion of subjects with low hemoglobin levels during screening. Subjects will be advised of these risks.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
-- Structured Clinical Interview for DSM-5 (SCID-5)
-- Columbia Suicide Severity Rating Scale (CSSRS)
-- Positive and Negative Syndrome Scale (PANSS)
-- Clinical Global Impression-Severity (CGI-S)
-- Medica history
-- Physical examination
-- Laboratories for basic chemistries, blood counts, liver function tests, urinalysis, urine toxicology, serum pregnancy test for women, thyroid tests
-- Electrocardiogram (EKG)
-- [18F]FPEB mGluR5 PET imaing
-- Structural MRI for co-registration of PET scan

If during the course of interviewing and assessment procedures, study staff identifies a condition that mandates immediate clinical intervention or official reporting (e.g., homicidality/suicidality), or that the participant is at significant risk for self or other destructive behavior, a study physician will be contacted and necessary treatment steps will be taken (e.g., hospitalization, continuous observation, referral to a care provider, etc.). All study MD's, including the Study PI will be available to the subjects and study staff 24 hours a day via their 24-contact numbers.
Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Radiolabeled drug/compound

Off label and investigational use of devices

Off label and investigational use of radiolabeled drugs/compounds

Radiolabeled Drug/Compound #1

Name of the radiolabeled drug/compound
[18F]FPEB
Manufacturer and other information
[18F]FPEB will be manufactured on site.
Approval Status

IND is approved
IND#
126935
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Lieberman, Jeffrey, MD

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
Not applicable

Clinical Treatment Alternatives

Clinical treatment alternatives
Not applicable.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Risks associated with the study are related to: a) PET scans with [18F]FPEB; b) arterial line placement; c) MR scans; d) intravenous catheter; e) blood sampling; f) interviews; g) inpatient research stays.

Yearly Cumulative Radiation Exposure:

The total possible exposure resulting from the study (5 mCi) will remain well below the FDA 21 361.1 dose limits for yearly cumulative exposure to research subjects (dose limits of 3 rads per single study, 5 rads per year for whole body, active blood forming organs, lens of the eye and gonads; 15 rads per year for other organs). The mass limit of [18F]FPEB will be 0.93 ug. Subjects exposed to radiation in the work place are excluded, as well as subjects exposed to nuclear medicine procedures during the previous year, including research protocols. In case of previous exposure to radioactivity due to research studies, subjects will be eligible if all conditions listed below are fulfilled:

1) The research studies in question have been performed in the context of a protocol from the Division of Translational Imaging (Anissa Abi-Dargham, M.D., Director) or as part of a research study within another division at Columbia University/NYSPI or at another institution, and the injected dose and dosimetry of the radiotracer are known.

2) Except for research studies, the subject has not been exposed to radiation during the past year (workplace

and medical).

3) Adding the previous exposure to the exposure due to the study will result in a yearly cumulative exposure lower than the limit defined by the FDA for research subjects (see above).

Arterial Line Placement:

A radial arterial catheter will be inserted for the PET scans associated with this study. Arterial sampling may be associated with mild-to-moderate pain or bruising at the puncture site. In rare instances blocking of the artery, poor healing, hematoma, inflammation, or infection at the catheter insertion site may occur. Certain individuals may feel light-headed during arterial catheter placement.

Table 1 provides the absorbed radiation dose calculation for [18F]FPEB. The data are based on a study by Wong et al., 2013 in J Nuclear Med.

The maximum injected dose will be 5mCi, and the rads this represents are listed in the dosimetry table below

Table 1. [18F]FPEB

Target organ	μSv/MBq	mrem/mCi	rem/5mCi
Adrenals	13.9 ± 1.5	51.6 ± 5.5	0.258
Brain	20.2 ± 6.8	74.6 ± 25.1	0.373
Red marrow	11.6 ± 1.0	43.0 ± 3.7	0.215
Osteogenic cells	15.7 ± 1.4	58.1 ± 5.1	0.2905
Skin	7.7 ± 0.9	28.5 ± 3.5	0.1425
Spleen	8.3 ± 0.8	30.8 ± 3.0	0.154
Testes	9.8 ± 1.5	36.2 ± 5.4	0.181
Thymus	9.6 ± 1.3	35.7 ± 4.9	0.1785
Thyroid	8.0 ± 0.7	29.6 ± 2.8	0.148
Urinary bladder	52.3 ± 12.2	175.2 ± 77.0	0.876
Uterus	16.9 ± 1.9	62.5 ± 6.9	0.3125
Total body	12.0 ± 0.2	44.4 ± 0.6	0.222
Equivalent dose	30.9 ± 13.1	114.4 ± 48.6	0.572
Effective dose	16.9 ± 1.8	62.4 ± 6.8	0.312
Breasts	8.1 ± 0.9	29.9 ± 3.4	0.1495
Gallbladder wall	191.4 ± 210.4	708.1 ± 708.1	3.5405
Lower large intestine wall	21.1 ± 4.6	78.1 ± 17.2	0.3905
Small intestine	40.0 ± 11.7	147.8 ± 43.3	0.739
Stomach wall	12.9 ± 0.5	47.7 ± 1.9	0.2385
Upper large intestine wall	44.4 ± 13.1	164.3 ± 48.5	0.8215
Heart wall	9.9 ± 1.5	36.7 ± 5.5	0.1835
Kidneys	17.3 ± 5.6	64.0 ± 20.9	0.32
Liver	41.1 ± 28.2	152.1 ± 104.4	0.7605

Lungs	10.3 ± 0.7	38.0 ± 2.8	0.19
Muscle	10.4 ± 0.9	38.6 ± 3.3	0.193
Ovaries	16.5 ± 2.3	61.0 ± 8.6	0.305
Pancreas	15.4 ± 1.9	56.9 ± 6.9	0.2845

The mass limit of [18F]FPEB will be 0.93 ug.

For this study, the maximum allowable injectable dose of [18F]FPEB will be 10 µg.

MR Scans:

There are no known long-term biological risks from the use of MRI scanners per se, including the General Electric (GE) 3T scanner for use in this proposal. The 3T GE system proposed in this study is a non-significant risk device, per U.S. Food and Drug Administration (FDA) website, Center for Devices and Radiological Health, "Guidance for the Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices", Nov., 1998).

At the same time, possible risks associated with MRI scanning can be classified into one of six areas: a) Acoustic Noise Levels; b) physical discomfort; c) fetal exposure; d) static magnetic fields (leading to the attraction of ferromagnetic metal objects); e) Gradient or Time Varying Magnetic Fields (leading to the possible stimulation of peripheral nerves); and f) Radiofrequency (RF) Magnetic Fields (leading to the possible risk of tissue heating).

a) Acoustic Noise Levels: The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process.

b) Physical Discomfort: The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress

c) Fetal Exposure: The risk of MR imaging to the fetus is unknown.

d) Static Magnetic Fields: The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with thousands of clinical studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the subject.

e) Time-Varying Magnetic Fields: The concern about the time-varying magnetic fields used in MRI is that these can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling'. In very rare instances, this nerve stimulation can be painful. Nerve stimulation is particularly likely when subjects are physically positioned in a way that increases the likelihood of inducing stimulation, such as with hands clasped or arms folded. It should be noted that the parameter of interest

here, dB/dt (the rate of change in the magnetic field per unit time), is not a function of the strength of the static magnetic field, so evaluating risk in a 3T MRI scanner involves the same considerations as evaluating other MRI systems operating at lower magnetic field strengths (i.e., the same issues apply to all the commercially available, FDA-approved scanning systems). Thus, it is the gradient system only that needs to be evaluated to determine the risk of producing nerve stimulation.

f) SAR: MRI scanning induces some heating of body tissues. This SAR that determines heating is the amount of radiofrequency (RF) energy deposited (typically by a coil or "helmet"-like apparatus placed over the subject's head) per unit volume of tissue per unit time. The SAR for RF radiation is primarily related to the amplitude of RF power, duration of the RF pulse, type of RF coil, frequency of RF radiation, resistivity of the tissue, configuration of the anatomical region, and several other parameters.
Describe procedures for minimizing risks

In the event that a subject deteriorates during the trip from Strasburg, PA to CUMC in New York City, the safety plan includes the following components:
-- The study coordinator will meet with the subject and the unaffected healthy 1st- or 2nd degree relative at the Strasburg office prior to departure for CUMC.
-- Dr. Markx will be at CUMC to meet with the patient and his/her family member as soon as they arrive.
-- The subject and unaffected family member will be given an emergency/off-hours contact number where they can reach Dr. Markx at any time during travel from Starsburg to CUMC in New York City.

Toxicology for [18F]FPEB:

To our knowledge, there are currently no reports of pharmacological effects from previous studies using an equivalent mass dose of [18F]FPEB to our study, thus we do not expect any pharmacological effects of [18F]FPEB.

The dose of radiation for [18F]FPEB will be submitted for approval to the Joint Safety Radiation Committee (JRSC). To further minimize risks of PET scanning, all scans will be done in the presence of medical supervision and trained nursing staff in an imaging center specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to a consultation with specialized medical units at New York Presbyterian Hospital Preparation of radiopharmaceuticals and performance of PET scans will be by radiochemists, physicians, and technologists of the Department of Radiology at CUMC. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The information on the previous radiation exposure of study subjects will be notified to the study doctor.

Arterial Line Placement:

Our group and others recently reviewed safety data from 1132 arterial lines placed in 924 PET research subjects through the NYSPI (24). There was a single incidence of symptomatic thrombotic occlusion, documented by Doppler ultrasound in a depressed female patient (incidence = 0.09%). There was no associated ischemic damage, and the condition resolved over a period of weeks without intervention. No

infections at the puncture site occurred. In a review of the literature between 1978-2001, Scheer found that among 19,617 radial artery catheterizations, thrombosis persisted as a major complication in just 0.09% of the cases (25). Among the 19,617 radial arterial cannulations reviewed by Scheer, septic complications occurred in 0.13% of cases. In the proposed study, arterial catheters will remain in place no more than 8 hours. (That includes the full time for the study, plus an estimate of maximal delay time.) In the event of such delays, subjects will be informed of the reason for the delay as well as an estimate of the duration of the delay.

Risks of radial artery cannulation are minimized by having the procedure performed by an experienced physician. Pain is minimized by local anesthesia. Bleeding is prevented by local pressure applied for a minimum of 15 minutes after catheter removal. Subjects will have their hand and finger blood supply examined after arterial cannulation and again following catheter removal. Also, subjects will be asked to abstain from using aspirin, NSAIDS or anticoagulants. Subjects will be provided a 24 hour emergency physician telephone number to call if they encounter pain, discoloration, numbness, tingling, coolness, hematoma, inflammation, or any other unusual symptoms in the wrist or hand, or fever, chills or drainage from the vascular puncture sites, following the procedure. Subjects will be instructed on what problems to watch for and procedures to follow should such problems occur. Infection is avoided by adequate cleansing of the skin prior to intravascular line insertion.

MR Scans:

Acoustic Noise Level:

FDA Guidelines: "The acoustic noise levels associated with the device must be shown to be below the level of concern established by pertinent Federal Regulatory or other recognized standards setting organizations. If the acoustic noise is not below the level of concern, the sponsor must recommend steps to reduce or alleviate the noise perceived by the patient." Current FDA guidelines follow the regulations of the International Electrotechnical Commission Standard 601-2-33, which stipulates that for MR equipment used in medicine, hearing protection is required when the system can produce acoustic sound levels above 99 dBA (maximum A weighted r.m.s.) and that the protection should be able to reduce noise levels to below 99 dBA. The FDA has approved systems for which noise levels have been quantified, ranging up to 105 dB RMS for scanners operating at field strengths of 3 Tesla. It is important to note that the static magnetic field strength is only one factor, and not necessarily the most important one, in determining acoustic noise. Among the factors listed above, the design and construction of the gradient coils plays a major role in the noise level that MRI scanning produces. Therefore, noise levels are not necessarily greater when scanning at 3 T field strengths. It is nevertheless possible that, in some circumstances, our system could produce noise levels higher than 99 dB, as do many clinical systems operating at lower field strengths.

The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA.

Static Magnetic Fields:

FDA Guidelines: “Studies conducted at 8T or less are not considered significant risk" (FDA Center for

Devices and Radiological Health, memorandum 7-14-03).

This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI units). It is not unique to our 3 Tesla facility, which will maintain a safety policy to safeguard subjects and staff members from these incidental risks. Systems with static magnetic fields less than 8 Tesla have been considered to represent a non-significant risk by the FDA. The static magnetic field of our system (3 Tesla) is therefore to be classified as posing non-significant risk to human subjects.

Time-Varying Magnetic Fields:

FDA Guidelines: The FDA Guidance of 1995 was developed specifically to consider the fact that many clinical systems were capable of exceeding levels of dB/dt that could produce nerve stimulation. It was originally considered that a warning level should be implemented to guard against peripheral nerve stimulation, but the FDA finally concluded that: 'this warning level is not considered critical since there are no harmful effects associated with mild peripheral nerve stimulation'. The current guidelines therefore include monitoring procedures to help avoid painful peripheral nerve stimulation, and without specific dB/dt limitations.

The gradients used in our 3 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances, the system will be operated in a way that poses non-significant risk to the participant.

SAR:

FDA Guidelines: "The following are levels of concern: A) If SAR # 0.4 W/kg whole body; and if SAR # 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR # 3.2 W/kg averaged over the head: below level of concern. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: below level of concern. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern."

This guideline is based on the calculation of a system that has no thermoregulatory response, and thus it is a very conservative estimate compared with the temperature change that would be experienced in any living subject. Normal diurnal temperature variations in humans, for example, are about +/-1°C from the normal set point 37°C, and healthy people with normal thermoregulatory responses can easily dissipate any excess (or, in this instance, deposited) heat by increasing their peripheral blood flow or sweat rate. Thus, the heating effect of MRI with the SARs used in accord with these guidelines is extraordinarily unlikely to cause any acute effects in healthy human subjects. Furthermore, our scanner console calculates SAR based on the subject's body weight before running any pulse sequence and prohibits running of the sequence if exceeds the FDA-approved limit.

Because all experiments performed on the 3 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, this criterion for classification of NSR is satisfied.

Summary of Minimizing Specific Risks Posed by MRI scanning:

The 3 Tesla scanner satisfies FDA criteria for nonsignificant risk in all risk categories. The following steps are taken to minimize risk:

Acoustic Noise: As suggested by the FDA, we take steps to reduce the noise levels experienced by subjects. The easiest and most reliable means of preventing hearing loss is to use disposable earplugs, which we will do for all scans. We will also be using acoustically shielded headsets, which further attenuate noise.

Physical Discomfort: All subjects will be able to communicate directly with technologists and study staff to inform them of any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately and the subject will be removed from the scanner.

Fetal Exposure: While there is no known risk of MR scans to the fetus, it is standard practice to exclude women who are pregnant from research MR scans. Therefore, to implement this exclusion a pregnancy blood test is performed at screening and, in addition, a urine pregnancy test is performed on the day of each MR scan for all female participants.

Static Magnetic Fields: These risks are the same as in other commercially available clinical systems. Like clinical MRI centers, our facility has a complete range of procedures to assure security of the restricted access area, careful screening of potential subjects before they enter the restricted access area, and a metal detector positioned at the doorway leading into the magnet room within the MRI suite. In addition, access is tightly controlled, allowing only those personnel and research subjects who have legitimate reason to be there. Doors to the unit will be securely locked, with only MR technologists, physicists, or physicians controlling entry of ferromagnetic and other materials that could possibly cause harm to research subjects, personnel, or equipment. In addition, entry-ways to the unit will be labeled with clear visible signs warning of the presence of the magnetic field and the exclusion from entry by individuals with implanted metal objects such as prostheses, pins, clips, IUDs, etc.

Nerve Stimulation: The consent form will provide information about this risk. A record of dB/dt value will also be included with the imaging data to help in analysis of levels of peripheral nerve stimulation possibly perceived by subjects. In addition, we will conduct detailed calculations of the changes in magnetic field over time that our gradient system is capable of, and conservative values will be selected as limits that will be used to determine when special additional monitoring is indicated. In these cases, we will use the monitoring procedures recommended by the FDA. The gradient switching times and strengths will also be monitored together with the routine assessment of all electrical components of the system, as described previously.

In addition, MR technologists receive special training to prevent peripheral nerve stimulation. Before any scanning procedure that might stimulate peripheral nerves, a technologist will: inform the subject that

peripheral nerve stimulation may occur; describe the nature of the sensation to the subject; instruct subjects not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation; maintain constant verbal contact with the subject; instruct subjects to inform the MR technologist if they experience discomfort or pain; terminate the scan if the subject complains of discomfort or pain; complete a report of any incidents involving severe discomfort or pain, including describing the associated circumstances (imaging parameters, dB/dt value, level of pain, etc.), and submit this report immediately to the IRB.

SAR Absorption: The magnitude of temperature increase during MRI scanning is minimal. Increases are always within FDA guidelines, which include core temperature increases less than 1°C, as well as localized heating to less than 38°C in the head, 39°C in the trunk, and 40°C in the extremities. Our 3 Tesla system has in place a means to monitor RF power levels and ensure that energy deposition is sufficiently low to stay well within these guidelines for temperature increases. First, a "system security" unit is employed to integrate the output of the RF amplifiers. This integration takes into account the amplitudes and duty cycle of the transmitter. If system security detects an output that might exceed the guidelines noted above, it automatically shuts down the entire RF power system. Secondly, all pulse sequences are evaluated, based on calculations and sound scientific measurements, to ensure that SAR remains within FDA-approved guidelines, prior to their use in humans. Any experiment performed on our 3 Tesla system will comply with all FDA guidelines with regard to RF power deposition. Proper and routine monitoring of all RF electronics (e.g., coils, transmitters, system security, etc.) will be performed on a regular basis. All pulse sequences will be evaluated (by calculation and by valid scientific measurement) prior to use in humans.

Intravenous Catheter: Placement of IVs will be by a physician or nurse trained and certified in aseptic technique for catheter placement to minimize this risk.

Blood Sampling: Adverse effects of blood sampling will be minimized by exclusion of subjects with low hemoglobin levels during screening. Subjects will be advised of these risks.

Clinical Assessments: If subjects have emotional responses, appropriate psychological support is given.

Inpatient Research Stays:
We describe at length the isolation, boredom, and inactivity before volunteers sign the consent form, and thus far, we have not encountered problems in this area. Of course, participants are free to leave the study at any time and care is taken to be sure that this option is understood.

Confidentiality:
Violation of confidentiality regarding psychiatric condition may cause problems such as difficulty with employment or insurance coverage or personal embarrassment. Standard precautions will be taken to protect the confidentiality of all research participants, including coding all data and only entering codes (study I.D. numbers, initials and date of birth) in computerized databases. All paper records are kept in locked files in the investigators' offices with access limited to research staff. Only aggregate results are published. All study staff have been trained to current standards and certified in HIPAA regulations; they will carefully apply these standards to their work on this study.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Research Data and Investigator Medical Records:

Blood and urine samples, behavioral assessments, PET and
MRI acquisitions, and all other clinical data will be obtained from the subjects for specific research purposes. 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.

Special Precautions:

Data from medical records may also be used on occasion with appropriate permission. The information gathered, excluding identifying information, will be shared with co- investigators and staff involved in this study; otherwise the information remains confidential and will be used only for research purposes and in accordance with IRB regulations. 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 DVDs 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.

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, all subjects have already undergone genetic testing for the CNTNAP2 mutation by Dr. Kevin Strauss (who is a consultant on this study) at the Clinic for Special Children (CSC). We will therefore be able to recruit patients who are known to carry the CNTNAP2 mutation through referrals from the CSC. We are not collecting DNA and will not story any genetic samples in the NIH repository for this study.

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
This study does not offer direct benefit to participants, but is likely to yield generalizable knowledge about abnormal mGluR5 binding in patients with a specific genetic mutation who suffer from psychotic spectrum disorders. These findings may be generalizable to the general psychotic patient population and may lead to future treatment studies with therapeutic compounds that target the mTOR pathway.

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.

Volunteers will be compensated for time and research-related inconveniences. Compensation will be pro-rated for parts completed if subjects do not complete the study. Subjects will be paid in either check or cash. If they receive a check, the check may be sent as late as after their participation in the study is complete. We will compensate for reasonable local travel expenses.

For participation in this study, subjects will receive:
- $30 for the screening visit
- $250 for the PET scan
- $100 for an arterial line
- $100 for the MRI scan
- $170 for the clinical assessment (approximately 1-4 hours)

Thus, the maximum total compensation for completion of the protocol is approximately up to $650. Patients will only receive compensation for procedures that they complete for this study.

Furthermore, a family member who accompanies you on your visit to both our Strasburg office as well as the visit to NYSPI/CUMC will receive $100 for each visit. Thus, the maximum total compensation for your family member who accompanies you on both trips is $200. Of note, this family member will not be a participant in the study.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of unbolded Information Sheet(s)
Upload copy(ies) of bolded Information Sheet(s)
Upload evidence of FDA Radiolabeled Drug approval(s)
Upload copy(ies) of JRSC approval(s)
Upload a copy of Certificate of Confidentiality
Upload copy(ies) of the HIPAA form
HIPAA Form (2016).pdf
Upload any additional documents that may be related to this study

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