Protocol Title: PET Imaging of brain mGluR5 receptors using [18F]SP203

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<table>
<thead>
<tr>
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<th>Number</th>
<th>Sex</th>
<th>Age Range</th>
</tr>
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<tbody>
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<td>Healthy controls</td>
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<td>18-65</td>
</tr>
</tbody>
</table>

Off Site Project: NO
Project uses ionizing radiation: YES
IND/IDE: YES Drug/Device/# IND not submitted yet
Sponsor: Robert Innis, MD, PhD
Project uses Durable Power of Attorney: NO
Data & Safety Monitoring Board: NO
Technology Transfer Agreement: NO
Samples are being stored: NO
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I. PRECIS

Metabotropic glutamate receptors are G-protein coupled receptors that respond to glutamate by activating proteins inside nerve cells that affect cell metabolism, thereby fine-tuning the signals sent between cells to maintain balance in neuronal activity. Metabotropic Glutamate receptors (mGluR5) are Group I receptors localized post-synaptically and found in several regions of the brain including the striatum, hippocampus, amygdala, and cortex. Activation of mGluR5 stimulates phospholipase C, resulting in phosphoinositide hydrolysis and increase of intracellular Ca\(^{2+}\) levels. Several potent antagonists for mGluR5 have been developed, including 6-methyl-2-(phenylethynyl)pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4yl)ethynyl] pyridine (MTEP) however, no simple derivatives of MPEP or MTEP had proven to be useful for \textit{in vivo} imaging.

In the present protocol, we will use a new PET ligand \([18F]SP203\) for two reasons: Phase 1.) we will perform kinetic brain imaging to quantify mGluR5 binding parameters in brain and determine the reliability and reproducibility of these measures in 15 healthy controls Phase 2.) if the tracer is proved successful in phase 1 we plan to estimate radiation-absorbed doses of \([18F]SP203\) in healthy human subjects by performing whole body imaging.

Successful development of a PET ligand to image mGluR5 will have a strong impact on clinical management of brain disorders with disruptions in glutamatergic transmission such as schizophrenia, anxiety, and neurodegenerative disorders including Alzheimer’s and Parkinson’s disease.

II. INTRODUCTION

A. Background

Glutamate is a ubiquitous excitatory neurotransmitter within the central nervous system (CNS) of mammals and act on numerous receptors, all with potential to modulate neurological function, mental state, and behavior. Glutamate receptors therefore represent attractive targets for drug development. In addition, there is a need to develop radioligands that are useful for selectively imaging glutamate receptors in living brains, so that their roles in health and neuropsychiatric disorders can be better elucidated. Such radioligands may themselves become useful for drug discovery and assessment of the efficacy of neuropsychiatric therapies and treatments.

Modulation of mGluR5 receptors has proven useful in the treatment of schizophrenia and Alzheimer’s disease (Tsai et al., 2005). Further evidence supports the use of MTEP in the treatment of anxiety (Brodkin et al., 2002), depression (Cosford et al., 2003), and pain (Walker et al., 2001). Metabotropic glutamate receptors subtype 5 also play an important role in drug-related behaviors, particularly in drug abuse (Tessari et al., 2004), addiction, and alcohol withdrawal(Kenny and Markou, 2004). Hence, mGluR5 antagonists may turn out to be useful therapeutics for a variety of CNS disorders.

MPEP and MTEP have provided leads to some candidate radioligands for imaging human mGluR5 receptors with PET \textit{in vivo}(Hamill et al., 2005). However, due to the small size and low degree of functionalization of MPEP and MTEP, labeling of their derivatives with an imaging radionuclide (\textit{e.g.} carbon-11, \(t_{1/2} = 20.4\) min; fluorine-18, \(t_{1/2} = 109.7\) min; iodine-123, \(t_{1/2} = 13\) h), so that the favorable pharmacology of high mGluR5 receptor affinity and selectivity is retained, is often a challenge. Until recently, no simple derivatives of MPEP or MTEP had proven to be useful for \textit{in vivo} imaging. In rat and monkey studies it was found that both \(^{11}\text{C}\)-labeled methoxy-MPEP and MMTEP gave the desired rapid uptake of radioactivity into brain. However, this uptake was immediately followed by fast washout. Moreover, these radioligands showed a uniform distribution across most cerebral regions.
Recently we developed, (3-fluoro-5-[(2-\[^{18}F\]fluoromethyl-thiazol-4-yl)ethynyl]benzonitrile) \[^{18}F\]SP203 which is a new easily synthesized candidate radioligand for imaging mGluR5 with PET. This ligand showed very high uptake in regions identified as having high densities of mGluR5 receptors in non-human primates. 

\[^{18}F\]SP203 will be assessed based upon the amount of brain uptake, the ratio of uptake in target (e.g., striatum; region known contain high densities of mGluR 5 receptors) and background regions (e.g., cerebellum and occipital cortex), and the identifiability of distribution volume measured with a compartmental modeling.

### III. STUDY OBJECTIVES

A. Objective

The protocol has two objectives:

1. **Part 1** to test the accuracy of mGluR5 binding parameters in brain using \[^{18}F\]SP203 PET imaging with arterial data in healthy volunteers;
2. **Part 2** if phase 1 is successful; we will estimate radiation-absorbed doses of \[^{18}F\]SP203 in healthy human subjects by performing whole body imaging.

### IV. SUBJECTS

A. Subjects/Study design

We will select fifteen healthy adult female and male volunteers (age 18–65 years old) for brain imaging and ten healthy volunteers for whole body dosimetry analysis. We will exclude children or minors because this study involves radiation exposure. The proportion of ethnic minorities (vs. Caucasians) in the total sample will approximately be consistent with the overall U.S. population proportions.

B. Inclusion criteria

Healthy control subjects aged 18–65 years, with history/physical exam, ECG, and laboratory tests within one year of the PET scan within normal limits.

C. Exclusion criteria

1. Current psychiatric illness, substance abuse or severe systemic disease based on history and physical exam.
2. Laboratory tests with clinically significant abnormalities.
3. Prior participation in other research protocols or clinical care in the last year such that radiation exposure would exceed the annual limits.
4. Pregnancy and breast feeding.
5. Claustrophobia. (part 1 only)
6. Presence of ferromagnetic metal in the body or heart pacemaker. (part 1 only)
8. consumed alcohol within 48 hours before the PET scan

D. Eligibility Checklist Appendix III
V. STUDY DESIGN AND METHODS

A. Study Sections 1&2

This study will proceed in two parts. In Part 1, to assess the accuracy of measuring mGluR5 receptor levels by dynamic brain PET imaging using $[^{18}F]$SP203; we will perform a quantification study in 10-15 normal subjects. We will quantify mGluR5 binding parameters to determine the reliability of these parameters using $[^{18}F]$SP203. Injection dose in the first part of the protocol is expected to be 10 mCi based on whole body dosimetry of $[^{18}F]$SP203 in rhesus monkeys.

In Part 2, in which we will only proceed if phase one results show stable values of receptor density measures as distribution volume calculated with compartmental modeling. Human dosimetry of $[^{18}F]$SP203 will be estimated by performing whole body imaging studies in 10 healthy subjects (5 males and 5 females). Our available human dosimetry data has been estimated from non-human primate biodistribution studies. Injection dose in this second part of the protocol is expected to be approximately 5 mCi based on the results of the whole body imaging studies in rhesus monkeys.

This protocol entails three components for each phase:

**Part 1** Evaluation, MRI, and PET. The MRI will be obtained within one year of the PET scan, i.e., up to one year before or one year after the PET scan. Healthy subjects will have an initial visit(s) for evaluation: physical/history, laboratory screening tests. Evaluation and PET sessions will take approximately 7 h.

**Part 2** Evaluation, PET scan, and post-scan safety monitoring laboratory tests will be administered. Twenty-four hour urine will be collected starting at the time of injection of the tracer on the day of the PET scan. Evaluation and PET sessions will take approximately 7 h.

i. Recruitment

The healthy subjects will be recruited and screened at NIH. We will use information from the NIH healthy volunteer office to assist with recruitment.

ii. Screening

Healthy volunteers will be screened at NIH, an EKG will be obtained, subjects will be asked to provide blood and urine samples for a battery of laboratory screening tests such as complete blood count including platelet count, chemistries (Na, K, Cl, HCO$_3$, BUN, Cr, glucose, Ca, PO$_4$, SGOT, SGPT, LDH, alkaline phosphatase, CPK, bilirubin, total protein, albumin), RPR, urinalysis, and urine drug screen. All women of child bearing potential will have a blood or a urine pregnancy test within 24 h prior to the PET scan.

iii. Study Design

**PET Procedure**

The NIMH Radiochemistry Laboratory (Dir., Victor Pike, PhD) will synthesize and perform QC (quality control) for $[^{18}F]$SP203. All women for this study (18 - 55 years old) will have a blood or a urine pregnancy test again within 24 h prior each PET tracer injection.

**Part 1 Kinetic Brain Imaging**

PET dynamic brain scanning will be performed using the GE Advance or HRRT in the PET Department. Subjects will be placed on the scanner bed with his/her head held firmly in place with a thermoplastic mask fixed to the bed. One antecubital venous and one radial arterial catheter will be placed. One venous catheter is for radioligand injection and the arterial catheter
is for blood sampling. Another additional antecubital venous catheter may be placed for blood sampling. Prior to the PET scanning, blood sample will be drawn for the laboratory tests, then a transmission scan will be performed with a $^{68}$Ge rotating pin source to provide a measured attenuation correction. The radiation-absorbed dose from a transmission scan was estimated to be 0.05 rad to the red marrow, lens of eyes, thyroid, and the brain (based on measurement by M. Daube-Witherspoon, Ph.D., memo of Nov 29, 1994). The radioligand (10 mCi of $[^{18}F]$SP203) will be injected intravenously as a bolus injection. The dosage of 10 mCi of $[^{18}F]$SP203 was selected for a few reasons. First, it is quite safe from a radiation safety perspective and would cause an estimated ED of ~0.6 rem. In addition, this is an exploratory IND with the purpose of determining whether the tracer is useful for imaging mGluR5 receptors in healthy controls. For this purpose, we plan to scan for 5 hours — i.e., 2.7 half-lives. The latter portions of the brain time activity curve will be particularly important to examine for the presence of radiolabeled metabolites (which would be evidenced by an increasing transient volume of distribution). Finally, we hope to obtain plasma measurements of parent radiotracer and metabolites for the entire period. We need to start with adequate activity to have measurable amounts at the end of the experiment.

PET images will be acquired in the three-dimensional mode with increasing length of frame for a total duration of 5 h. Following the transmission scan, 10 mCi of the tracer will be injected intravenously as a bolus and PET images will then be over 5 hours. PET images will be obtained continuously for approximately 120 minutes. The first scanning session will last about 2 hours, followed by 30 minute break and two one hour scan sessions. This sequence of scanning sessions will occur until approximately 5 h post injection. The subjects can come out of the camera between scans. Therefore, the total length of image acquisition will be approximately 4 h. To reduce radiation-absorbed dose to the urinary bladder wall, subjects will be instructed to void once every two hours.

To measure input function of the radioligand, blood samples will be obtained frequently from the arterial line. Several venous samples may also be obtained at several time points to estimate arterial input function using venous blood data. Blood sampling volume will be no more than 250 mL.

Part 2 Whole Body Imaging

Both a pre-injection transmission scan and a series of dynamic emission scans were acquired using a GE Advance tomograph (GE Medical Systems, WI). The PET device was calibrated daily with a $^{137}$Cs source and cross-calibrated weekly to a well counter using a known amount of $^{18}$F activity contained in a 16-cm diameter, cylindrical phantom. Each subject was imaged in seven contiguous 15-cm segments from the top of the head to a point below the gonads that varied depending on the height of the subject. To minimize extraneous motion, all subjects wore a mask that affixed their head in a single position and have their arms and abdomen wrapped with body-restraining sheets. This may add some additional discomfort.

Blood pressure, pulse, and respiration rates were obtained prior to the administration of $[^{18}F]$SP203 and at three time points during the emission scans.

Before injection of the radioligand, a 21 min transmission scan (3 min at each of the 7 body segments) using rotating $^{68}$Ge rods was acquired for subsequent attenuation correction. Then, an initial set of dynamic emission scans consisting of 14 cycles was acquired following the intravenous injection of $192 \pm 7$ MBq ($5.2 \pm 0.2$ mCi) $[^{18}F]$SP203.

The acquisition of each cycle began with an emission scan at the first bed position (i.e., the head), and continued by moving the bed distally to the next body segment for a total of seven segments. The scan of the seventh segment completed a cycle, and the bed
was moved back to the original position. The length of time that each segment was imaged within each of the 14 cycles varied as follows: 4 x 0.25, 3 x 0.5, 3 x 1, 3 x 2 and 1 x 4 min. The 6 movements of the bed between segments 1 through 7 required 3 s each, and the repositioning of the bed following the completion of each of the cycles required 13 s. Thus, the total length of the initial emission scan was about 120 min.

Following the completion of the first emission scan, the subjects were allowed to rest for about 30 min. During this time, all voided urine was collected for measurement of radioactivity. The subject then returned to the scanner and was positioned in, and affixed to, the same approximate location on the bed as for the first scan. A second 21 min transmission scan, identical to the first, was performed followed by a second set of dynamic emission scans that began about 3 h after injection of radioligand. The emission scan consisted of 2 cycles with segment imaging times of 4 min each for a total scan time of about 60 min. After completing all scans, the subject was asked to void before leaving NIH so the activity in urine could be measured. The subject went home with a 24-h urine collection container, and we measured urine radioactivity the next day. Radioactivity was measured with a gamma counter that was cross-calibrated with the GE Advance scanner.

Safety monitoring of subjects

The pulse rate, temperature, blood pressure, respiratory rate, and ECG will be recorded within 3 h before tracer injection, and again at about 15, 30, 90, 120, and 180 min after tracer injection. Neurobehavioral assessment will also be recorded within 3 h before tracer injection, and repeated at about 30 and 120 min after tracer injection. The screening laboratory tests (excluding pregnancy test) described above will be repeated ~24 h after tracer injection. If the subject cannot come at the above mentioned time point, the blood and urine samples will be taken shortly after the PET procedure.

MRI procedure (Part 1 only)

Subjects will have an MRI scan for anatomical localization by coregistering onto PET image. MRI scanning will be performed at the NIH Clinical Center and takes about one hour. If subjects become anxious during a scan, lorazepam (Ativan® 0.5–1mg) may be administered orally. If this medication is given, there will be at least a one week interval between MRI and PET scans. All subjects must meet the inclusion and exclusion criteria listed in Section IV – Subject Enrollment.

iv. Study Procedures

The duration of this study is two years. All subjects will undergo the approximate schedule of visits as described in the Table below.

**Part 1:**

<table>
<thead>
<tr>
<th>Brain imaging study</th>
<th>1st Visit – Screen</th>
<th>2nd Visit</th>
<th>3rd Visit</th>
<th>4th Visit</th>
</tr>
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<tbody>
<tr>
<td>Time - weeks</td>
<td>0</td>
<td>≤24</td>
<td>≤24</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Physical Exam  ×  
Neurological Exam  ×  
Pregnancy test (female ≤ 55)  ×  ×*
MRI  ×**
Brain PET  
Blood and urine tests  ×  ×  ×#

*A serum pregnancy test will be done within 24 h prior to the PET ligand administration.
**Depending on the availability of PET and MRI scanners, an MRI scan may be scheduled at any point in time for this protocol, either before or after the PET procedures.
#The blood and urine samples will be taken ~24 h after PET procedure. If the subjects cannot come to the Clinical Center at above mentioned time, the blood and urine samples will be taken shortly after the PET procedure.

**Part 2**

Human dosimetry will be estimated by performing whole body imaging in 10 healthy subjects (~ 5 males and 5 females). On the first visit, the subjects will be screened for eligibility. On the second visit, whole body PET scanning will be performed. On the third visit, the day after the PET scan, routine safety monitoring such as CBC, Chem 20, thyroid function tests and routine urine analysis will be performed Twenty-four hour urine will be collected starting at the time of injection of the tracer on the day of the PET scan. Study schemas are shown below.

<table>
<thead>
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<th>Whole body imaging (Part 2)</th>
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<tr>
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<tr>
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<tr>
<td>Time - weeks</td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Physical Exam</td>
</tr>
<tr>
<td>Pregnancy test (female ≤ 55)</td>
</tr>
<tr>
<td>PET whole body imaging</td>
</tr>
<tr>
<td>Blood and urine tests</td>
</tr>
</tbody>
</table>

**[18F]SP203 Source**

The NIMH Radiochemistry Laboratory will synthesize and perform QC (quality control) on the tracer [18F]SP203 in accordance with IND. As for other IND agents synthesized at the CC PET Department, the FDA grants authority for such synthesis and QC. Furthermore, the FDA may inspect the process at any time.
Relevant pharmacology

SP203 is selective for mGluR5 receptors. Because of the tracer doses, no pharmacological effects are expected with $[^{18}\text{F}]$SP203.

Toxicity

Stanford Research Institute (SRI) performed an extended acute toxicity study in rats. The executive summary is provided below, and the complete report is located in Appendix.

The objective of this study is to determine potential toxic effects, and to identify potential target organs of toxicity for the toxicity endpoints examined following a single intravenous (iv) bolus administration of M1.

Male and female Sprague-Dawley rats (10/sex/group) were given a single iv dose of M1 at 88.1 μg/kg (528.6 μg/m², 100x human dose) on Day 1. A control group (10/sex) was given a single iv dose of vehicle (4.8% ethanol (v/v) and 2.8% (v/v) Cremophor EL in sterile saline) at an equivalent volume on Day 1. Animals were sacrificed on Days 3 and 15 (interim and terminal necropsy, respectively).

The following parameters were evaluated: mortality/morbidity, clinical observations, body weights, food consumption, clinical pathology (hematology and serum chemistry), organ weights, necropsy macroscopic observation and microscopic histopathology. All animals survived until their scheduled necropsy. No drug-related effects were observed for clinical observations, body weights, food consumption, clinical pathology, organ weights, macroscopic or histopathologic evaluations. Slight, sporadic changes in clinical pathology parameters did not correlate with histopathologic or other toxicologic parameters, and are considered to be of minimal toxicologic significance.

In conclusion, a single intravenous administration of M1 to male and female Sprague-Dawley rats at 88.1 μg/kg (100x human dose) did not produce overt biologically or toxicologically significant adverse effects. The maximum tolerated dose (MTD) is therefore considered to be greater than 88.1 μg/kg (528.6 μg/m²) and the no observed adverse effect level (NOAEL) is considered to be at least 88.1 μg/kg (528.6 μg/m²).

No effects, side effects or toxicity is expected from this radioligand, since it is administered at tracer doses.

Formulation and preparation

$[^{18}\text{F}]$SP203 will be synthesized at the radiochemistry lab of MIB/NIMH.

Stability and storage

$[^{18}\text{F}]$SP203 will be administered within 120 minutes after synthesis of the radioligand. The radioligand is stable during this period.

Incompatibilities

$[^{18}\text{F}]$SP203 will be administered at a tracer dose and no other medication will be involved in this protocol. Therefore, we do not expect pharmacological effects or interactions with concomitant medication the subject is taking.

Follow-up/termination procedures

There will be no follow-up services provided in this protocol.
Relationship to other studies proposed

None

VI. RISKS/DISCOMFORTS

This is a more than minimal risk study. Potential risks from this study include those associated with: 1) medical examinations including laboratory testing that may reveal previously undiagnosed medical disorders, 2) radiation exposure from the PET and transmission scans, 3) PET scanning, and 4) placement of arterial and venous line and blood sampling, 5) blood sampling and 6) MRI.

1. Medical Examination and Laboratory Testing

The potential risks of a medical examination are small but do include the detection of an otherwise undiagnosed disorder. We will first explain and familiarize the subjects with the laboratory testing to minimize discomfort, if any, during testing. In the present protocol, all healthy normal volunteers are expected to undergo recruitment and assessment procedures without any difficulties. However, if, in the opinion of the study staff, PI, or subject, the study participation is adversely affecting the subject's emotional and or physical well-being, the individual circumstances will be reviewed to determine what additional steps should be taken, such as termination of the study and making appropriate referrals to address their underlying health problems. If the subject desires not to proceed further with testing, we will end these sessions at any time point. Blood tests may lead to the formation of a small subcutaneous hematoma caused by blood leaking from a punctured blood vessel. This hematoma causes only minor discomfort. It is not dangerous and requires no treatment other than reassuring the patient. There is also a small risk of infection at the site of the needle puncture, which can be readily treated with antibiotic therapy. Approximately 25 mL of blood will be withdrawn for screening purpose.

2. Radiation Exposure Risks

Radiation exposure in this protocol will be from $[^{18}\text{F}]$SP203 and the $^{68}\text{Ge}$ transmission scan. The radiation-absorbed dose from a transmission scan is based on the measurement by M. Daube-Witherspoon, Ph.D., (memo of Nov 29, 1994). The radiation safety of $^{18}\text{F}$-labeled tracers is well established and results in an Effective Dose (ED) of approximately 0.06 rem/mCi. Thus, the proposed 10 mCi injection would cause a dose of ~0.6 rem, well below the NIH RSC guideline of 5 rem.

3. PET Scanning

PET scanning, which detects injected radioactivity within the body, is associated with no known physical hazards to the subject lying on the table. We routinely use a series of procedures to minimize the risk for discomfort during scanning sessions. Namely, the procedures are conducted in the presence of trained health professionals to whom subjects will have ready access, should they experience any problems. Subjects can communicate with the trained health professionals while in the scanner and can withdraw from the study at any time if they wish to do so.

Occasionally subjects become anxious during the scan. In that case, subjects can request the operator of the PET to stop the scan.

4. Arterial/Venous line Placement
Arterial catheterization has been shown to be a generally safe and reliable method to obtain arterial blood samples (Lockwood, 1985). Placement of a radial arterial catheter may cause bruising or infection. There is also a risk of occlusion and microemboli. In the past, over 3,000 arterial catheters have been placed in the PET department. Of these, two complications requiring physician’s care were reported. In the first case, a small radial artery aneurysm developed several months later, which was successfully repaired surgically. In the second case, a radial artery thrombosis developed 28 days later, which was also successfully repaired surgically. The arterial line will be placed by a member of the anesthesiology staff after confirming normal double circulation (both radial and ulnar arteries).

Venous catheter insertion, which is less invasive than arterial catheterization, can also be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize these risks.

5. Blood Sampling

Subjects will have no more than 250 mL blood sampling including that for lab tests. Subjects will be asked not to donate blood for a period of eight weeks after the participation is completed. The risks are associated with the arterial or venous catheterization as described in the previous section.

6. MRI

MRI is not associated with any known deleterious biological effects. 1.5 Tesla MRI is also widely used as a clinical imaging tool. Subjects will be screened and excluded for the presence of any metallic prostheses both at the time of recruitment and just prior to MR imaging. Subjects will wear ear-plugs to minimize exposure to excessively loud noises. Occasionally subjects become anxious during the scan. In that case, Ativan® 0.5-1 mg may be given per oral before MRI upon a request by subjects. Subjects can also request the operator to stop the scan.

Claustrophobic subjects find it difficult be scanned on MRI and subjects with this condition will be excluded at the time of recruitment.

VII. SUBJECT MONITORING

A. Parameters to be monitored

The pulse rate, temperature, blood pressure, respiratory rate, and ECG will be recorded within 3 h before tracer injection, and again at about 15, 30, 90, 120 and 180 min after tracer injection.

B. Toxicity criteria

There is no expected toxicity in this study.

C. Reasons for discontinuation from study

Scanning procedures will be stopped for any subject who asks to stop for any reason at any time. Subjects will be asked if they wish to continue the rest of the study. Subjects have the right to withdraw from this study at any time for any reason.

VIII. STATISTICAL ANALYSIS

Data of brain imaging studies will be analyzed with compartmental nonlinear least squares analyses and non-compartmental linear and multilinear regression analyses using arterial input function. Distribution volume (Bmax/Kd plus radioactivity not specifically bound to mGluR 5) will be calculated for brain regions known to contain high densities of receptors (e.g. striatum, hippocampus, and frontal cortices). PET derived parametric images and MR images will be
coregistered using MEDx (Multimodality Radiological Image Processing, Sensor System, Inc. Sterling, VA, USA).

IX. HUMAN SUBJECTS PROTECTION

A. Justification for the use of placebo, medication washout, or provocative stimuli
   This protocol will not involve the use of placebo, medication washout or provocative stimuli.

B. Concomitant clinical care
   None

C. Qualifications of investigators
   Investigators listed in this protocol are experienced in the execution of neuroreceptor PET imaging studies in humans.

D. Safeguards for vulnerable populations
   A serum pregnancy test will be done within 24 h prior to the PET ligand administration.

X. BENEFITS
   This study does not offer direct benefit to participants but is likely to yield generalizable knowledge about the density of mGluR5 receptors in the brains of healthy volunteers.

XI. SUMMARY/CLASSIFICATION OF RISK
   There is no direct benefit but likely to yield generalizable knowledge.

XII. CONSENT DOCUMENTS & PROCESS
   Study investigators will obtain informed consent. Each subject will receive an oral and written explanation of the purposes and potential risks of participation in this protocol. All subjects must be capable of providing independent consent for study participation.

   Subjects will be told that (a) the information derived may eventually lead to better understanding of brain chemistry and behavior; (b) PET imaging as used in this study is a research tool, hence no diagnostic interpretation will be given; (c) a confidential code number will be used to ensure that information cannot be linked or traced to any person or family; (d) data will be treated to group statistical analyses only; and (e) subjects will be given ample opportunity to ask questions of the investigators.

   For women of child bearing potential, a serum pregnancy test will be conducted within 24 h before the PET scan. Finally, when the laboratory tests and medical examination show significant abnormalities, appropriate referrals will be made to address their health problems. Consent will be obtained by the Principal Investigator or one of the Associate Investigators.

XIII. DATA & SAFETY MONITORING
   Data and Safety will be monitored by the lead associate investigator. Demographic and clinical data will be archived in EXCEL on a PC server. Imaging and blood data will be offloaded from the scanner/blood sampling device to a PC or a SUN workstation after each imaging session has been completed. Clinical Safety Monitoring data will be archived together with other data.

   The study will be terminated when we have collected sufficient data.
XIV. ADVERSE EVENT REPORTING
The lead associate investigator will report immediately all serious adverse events to the NIMH Clinical Director verbally, the NIMH IRB, and RSC verbally and in writing within the guidelines set by the NIH Standards for intramural clinical research.

XV. ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES
Subjects do not receive any treatment in this study or forego any treatment in order to participate in this study.

XVI. CONFIDENTIALITY
Every necessary step will be taken to prevent identification of study participants and other violations of subject confidentiality. Information will be stored using a confidential case number, and no identifiers (name, address, phone number, etc.) will be used that could allow direct linking of database information to individual subjects. Where temporary linking of information with identifiers is needed, such identifiers will be temporarily attached to the data, and will be removed after information has been encoded. Secured e-mail will be used for all electronic communications of subject information between investigators.

XVII. CONFLICT OF INTEREST/TECHNOLOGY TRANSFER
NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report.

XVIII. COMPENSATION
Reimbursement is based on NIH standards for time devoted to the research project. Subjects will be paid for each portion of the study they have completed whether or not they opt for early withdrawal from participation. (Please refer to Appendix I for breakdown of payment schedule.)

XIX. REFERENCES


XX. ATTACHMENTS/APPENDICES

I. APPENDIX: REIMBURSEMENT SCHEDULE (Part 1) Kinetic Brain Study

<table>
<thead>
<tr>
<th>Visit 1 (Outpatient)</th>
<th>Inconvenience Units</th>
<th>Pay for inconvenience (1)</th>
<th>Time (h)</th>
<th>Pay for time (2)</th>
<th>Total Pay (1 + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History taking, physical exams, blood tests, and urinalysis</td>
<td>7</td>
<td>$70</td>
<td>2</td>
<td>$30</td>
<td>$100</td>
</tr>
</tbody>
</table>

Visit 2 to NIH (Outpatient)

| MRI | 9 | $90 | 1 | $20 | $110 |

Visit 3 (Outpatient)

| PET scanning | 10 | $100 | 4 | $50 | $150 |
| Arterial catheter | 6 | $60 | | | $60 |
| Antecubital venous catheters | 3 | $30 | | | $30 |
| Serum Pregnancy test | 1 | $10 | | | $10 |
| Movement restriction | 1 | $10 | | | $10 |

Visit 4 (outpatient)

| Blood tests and urinalysis | 7 | $70 | 2 | $30 | $100 |

Total: $570

*The blood and urine samples will be taken ~24 h after PET procedure. If the subjects cannot come to the Clinical Center at above mentioned time, the blood and urine samples will be taken right after the PET procedure during the visit 3. Then total reimbursement will be $490.

(Phase 2) Whole body imaging

<table>
<thead>
<tr>
<th>Visit 1 (Outpatient)</th>
<th>Inconvenience Units</th>
<th>Pay for inconvenience (1)</th>
<th>Time (h)</th>
<th>Pay for time (2)</th>
<th>Total Pay (1 + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History taking, physical exams, blood test, and urinalysis</td>
<td>2</td>
<td>$20</td>
<td>2</td>
<td>$30</td>
<td>$50</td>
</tr>
</tbody>
</table>

Visit 2 (outpatient)

| PET scanning | 10 | $100 | 8 | $90 | $240 |
| Antecubital venous catheters | 3 | $30 | | | $30 |
| Serum Pregnancy test | 1 | $10 | | | $10 |
| Movement restriction | 1 | $10 | | | $10 |
| Vital signs and EKG | 2 | $20 | | | $30 |

Visit 3 (outpatient)

| Blood test and urinalysis | 2 | $20 | 1 | $20 | $40 |

Total: $410
### II. APPENDIX: Eligibility Checklist

<table>
<thead>
<tr>
<th>INCLUSION CRITERION</th>
<th>PET brain imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Healthy</td>
</tr>
<tr>
<td>Ages</td>
<td>18-65 y</td>
</tr>
<tr>
<td>laboratory tests, history/physical exam, and ECG and within one year of the PET scan within normal limits</td>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION CRITERION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current/history of psychiatric disease, substance dependence or traumatic brain injury, severe systemic disease, poor vision or hearing</td>
</tr>
<tr>
<td>History of substance abuse within 6 months</td>
</tr>
<tr>
<td>Abnormal laboratory tests, including HIV test</td>
</tr>
<tr>
<td>consumed alcohol within 48 hours before the PET scan</td>
</tr>
<tr>
<td>Any prior participation in other research protocols involving radiation exposure within the past year</td>
</tr>
<tr>
<td>Prior participation in other research protocols within the past year such that a radiation exposure together with the present study would exceed the annual limits</td>
</tr>
<tr>
<td>Pregnancy and Breast Feeding</td>
</tr>
<tr>
<td>Positive HIV test</td>
</tr>
<tr>
<td>Claustrophobia</td>
</tr>
<tr>
<td>Presence of ferromagnetic metal in the body or heart pacemaker</td>
</tr>
</tbody>
</table>

Limits: A total effective dose 5 rem in a year and 2.5 rad per year to the lens of the eyes, gonads and blood-forming organs; and 7.5 rad annually for all other organs.

Women with child bearing potential will have a serum pregnancy test to exclude pregnancy.

Part 1 only)
INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:
Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

PURPOSE

The metabotropic glutamate subtype five (mGluR5) receptor is a protein found in many places in the brain. It is the target for glutamate, which is an excitatory chemical messenger. The purpose of this protocol is to measure mGluR5 receptors in the brain by obtaining two kinds of brain pictures:

1) PET (positron emission tomography) can measure the number of target proteins after injection of a radioactive drug. In this case, we will inject a research radioactive drug called $[^{18}F]SP203$ that binds to mGluR5 receptors. This research drug is given at low doses, and we expect that you will not have any pharmacological (i.e., drug) effects.

2) MRI (magnetic resonance imaging) provides a picture of brain structure and will be used to identify the regions that are imaged with PET. This is the first time that the compound will be administered to human beings as such; there may be some minimal unanticipated effects.
QUALIFICATIONS

You are asked to participate in this study because you are a healthy subject. Females and males are invited to join this study. To be considered for participation, you must be 18 – 65 years of age and in overall good health.

You will not be able to participate in this study for any of the following reasons:

1. Current psychiatric illness, substance abuse or severe systemic disease based on history and physical exam.
2. Significantly abnormal laboratory results from blood and urine tests.
3. Previous radiation exposure (X-rays, PET scans etc.) that would exceed the RSC annual guideline.
4. Pregnancy and breast feeding.
5. Claustrophobia to a degree that you would feel uncomfortable in the MRI machine.
6. Presence of metal in the body or heart pacemaker.
8. A history of significant brain disease.
9. Cannot lie on your back for long periods since the pictures will be taken for about 4 hours during which time you will have to lie still on the scanner bed.
10. Consumed alcohol within 48 hours before the PET scan.

PROCEDURES

This study requires that you come to the NIH as an outpatient for three procedures that will require 4 visits: EVALUATION, MRI, PET, and the laboratory tests ~24 h after PET scan. The EVALUATION will be performed first under another protocol (01-M-0254), but the order of the MRI and PET visits may be interchanged, depending upon the availability of the instruments.

1) EVALUATION. During the evaluation visit, you will have a history and physical examination. The laboratory tests will include blood and a urine sample for illegal and addictive drugs. The history will include a detailed question on your psychological health. The EVALUATION will take approximately 3 hours.

2) PET Scan: On the day of the PET scan, first you will go to the Post-Anesthesia Care Unit (PACU) where anesthesiologist will insert arterial and venous lines into your arms. He will place one small plastic tube (called catheter) into a vein in your arm. We will use this tube for injection of the tracer. Anesthesiologist will also place another catheter into an artery in your wrist. He will first numb the area with Novocain prior to the placement to minimize discomfort. We will use this catheter to obtain arterial blood data during the scan. Both catheters will stay in place during the entire PET procedure. Next you will go to the Clinical PET Center, where your PET scan will be performed; there you will be met by a nuclear medicine technologist. You will be shown the scanner used for the procedure and you will have the opportunity to ask any remaining questions. Once you feel comfortable and are ready to continue with the scanning procedure, you will lie down on the scanner bed and a special mask will be fitted to your head and attached to the bed. This mask will be used to help keep your head in place during the procedure so that the images produced will be clear and easily interpreted. Just before injection of radioactive tracer, blood samples will be drawn for the laboratory tests. Then an 8-minute scan (called a “transmission” scan) will be performed. This is to provide measures of the brain that will help us more precisely calculate the information from the subsequent scans. After the transmission scan is completed, the radioactive tracer, [18F]SP203, will be injected into a venous catheter (i.v. line) in your arm. The scan will produce a “picture” of the mGluR5 receptors in your brain.

Pictures will be taken for about 4 hours during the 5 hours after injection of [18F]SP203. The first scanning session will last about 2 hours, followed by 30 minute break outside the camera, followed by about one hour in the camera, another 30 minute break, and a final one hour scanning session. During the scans, you will have to lie still on
the camera bed. During the breaks, you will be asked to go to the bathroom to void. This will eliminate radioactive urine to minimize your radiation exposure.

You will be asked to return to the Clinical Center for blood and urine tests ~24 h after the PET scan.

3) MRI: The MRI scan will be obtained within 1 year of the PET scan – that is, up to one year before or one year after the PET scan. On the day of the MRI, you will have to come to the Clinical Center at the time of your appointment. MRI uses magnetic fields and radio waves to give us pictures of actual structures inside the body—in this case, the brain. To perform the scan, you will lie on the scanner bed and placed inside the MRI scanner, which is a tube-like device. You will be asked to wear earplugs during the scan to protect your ears from the noise of the machine during the scan. Because the space inside the scanner is small, it sometimes causes people to be somewhat anxious. While you are inside the MRI scanner, we will be able to hear you speak. If you feel too uncomfortable during this procedure, you can tell us to stop the procedure. The entire scan will take about one hour.

HAZARDS AND PRECAUTIONS

Potential Risks

Potential risks or inconveniences to you associated with this study include: 1) radiation exposure from the PET and transmission scan, 2) PET and MRI scanning, 3) Arterial/venous lines placement and blood sampling.

1. Radiation Exposure Risks

You will be asked about any prior research participation involving radiation exposure so that your exposure would not exceed, in combination with the present study, a total effective dose of 5 rem per year, an annual limit established by the NIH Radiation Safety Committee for research studies. This limit does not include radiation exposure received for medical reasons.

This research study involves exposure to radiation from \(^{18}\text{F}\)SP203 and transmission scans. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation you will receive by completing participation in this study is from 10 millicuries from PET scan (a millicurie is a unit of measure of radioactivity) and from a \(^{68}\text{Ge}\) transmission scan. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving slightly greater than minimal risk and necessary to obtain the research information desired.

Since this is an exploratory IND compound, the whole-body biodistribution, radiation absorbed dose in human have not been studied yet. Based on animal studies, we estimate that you will receive a total of 2.0 rem to your lungs, 1.1 rem to your kidney, and 1.01 rem to your brain. All other organs will receive smaller amounts of radiation. We estimate that the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 0.6 rem. This calculated value is known as the “effective dose” and is used to relate the dose received by all organs in a single value. The amount of radiation received in this study is within the dose guideline recommended by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem per year.)

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth’s air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in two years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects
have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in your chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is approximately 0.02 percent. Therefore, your total risk of fatal cancer may increase from 25 percent to 25.02 percent. This change in risk is small and cannot be measured directly.

Please tell your doctor if you have been in research studies or received any medical care at the NIH or other places/hospitals that involved the use of radiation so that we can make sure that your total exposure from all studies is not too large. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant, suspect you are pregnant, or breast feeding, you may not participate in this research study. It is best to prevent or avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults. If you are a woman of child bearing potential, you must consent to have a pregnancy test before PET scanning to make sure that you are not pregnant or you may not participate.

2. PET and MRI Scanning

PET scanning, a procedure that is performed with the subject lying on the scanner bed, detects injected radioactivity within brain. There are no known physical hazards associated with this procedure. The special mask you will be required to wear during PET scanning is not associated with any danger but may be somewhat uncomfortable. However, because you must be completely still during the procedure, you may become somewhat uncomfortable or restless.

MRI is not associated with any known biological side effects and is used widely to diagnose and track illness in hospitals and clinics. You will be examined and excluded for the presence of any metallic implants both at the time of recruitment, and just prior to MR imaging. You will wear earplugs to minimize exposure to loud noises. Because the space inside the scanner is small, it sometimes causes people to be somewhat anxious. If you become too anxious during the scan, you can tell the operator of the MRI to stop the scan. If you are so claustrophobic that you find it difficult to be scanned by MRI, you will be excluded from this study at the time of recruitment.

3. Arterial/Venous Line Placement and blood sampling

Arterial catheterization has been shown to be a generally safe and reliable method to obtain arterial blood sample. Placement of a radial arterial catheter may cause bruising or infection. There is also a risk of occlusion and microemboli. In the past, over 3,000 arterial catheters have been placed in the PET department. Of these, two complications requiring physician's care were reported. In the first case, a small radial artery aneurysm developed several months later, which was successfully repaired surgically. In the second case, a radial artery thrombosis developed 28 days later, which was also successfully repaired surgically. The arterial line will be placed by a member of the anesthesiology staff after confirming normal double circulation (both radial and ulnar arteries).

Venous catheter insertion, which is less invasive than arterial catheterization, can also be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize these risks.

Subjects will have no more than 250 mL (about 1 pint) blood sampling including that for lab tests. Careful screening of health status will be done prior to the enrollment in the study. Subjects will be asked not to donate blood for a period of eight weeks after the participation is completed.

**BENEFITS**

There is no direct benefit to you for participation in this study.
PAYMENT

You will receive reimbursement based on NIH standards for time devoted to the research project. Maximum payment will be approximately $570 for the whole study. Payment will be made at the time of completion of the study. However, if you decide to stop the study early, or if the researchers decide that you should no longer participate, you will be paid for all visits or parts of visits that you have completed.

WITHDRAWAL FROM STUDY

You can voluntarily withdraw from the participation in this study at any time, including during scanning procedures, if you wish to do so. We may also decide to end your participation in this study if unexpected situations arise that indicate it is necessary to do so.

HIV Testing

As part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of your fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.
2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.
3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.
4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.
   a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.
   b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.
   c. The Clinical Center may report certain communicable diseases, including AIDS and symptomatic HIV infection, to appropriate State and Federal government agencies.
If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: (301) 496-2381.
OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Amira K. Brown Ph.D.; Building 1, Room B3-20, Telephone: 301-435-1695. Or Robert B. Innis, M.D., Ph.D., Building 1, Room B3-10, Telephone: 301-594-1089. You may also call the Clinical Center Patient Representative at (301) 496-2626.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient’s Consent
   I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

   Signature of Adult Patient/Legal Representative Date

B. Parent’s Permission for Minor Patient.
   I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
   (Attach NIH 2514-2, Minor’s Assent, if applicable.)

   Signature of Parent(s)/Guardian Date

C. Child’s Verbal Assent (If Applicable)
   The information in the above consent was described to my child and my child agrees to participate in the study.

   Signature of Parent(s)/Guardian Date

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM

Signature of Investigator Date Signature of Witness Date
INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:
Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

PURPOSE

The metabotropic glutamate subtype five (mGluR5) receptor is a protein found in many places in the brain. It is the target for glutamate, which is an excitatory chemical messenger. Our goal is to determine how the radioactivity is distributed in the body after injection as well as how it is broken down in the body. This will allow us to better determine appropriate doses for future studies. This is the first time that the compound will be administered to human beings, as such; there may be some minimal unanticipated effects.

QUALIFICATIONS

As a volunteer, you must be a healthy male or female, age 18-65, with no current medical or psychiatric illness (including substance abuse disorder).
You are asked to participate in this study because you are a healthy subject. Females and males are invited to join this study. To be considered for participation, you must be 18 - 65 years of age and in overall good health.

You will not be able to participate in this study for any of the following reasons:

1. Current psychiatric illness, substance abuse or severe systemic disease based on history and physical exam.
2. Significantly abnormal laboratory results from blood and urine tests.
3. Previous radiation exposure (X-rays, PET scans etc.) that would exceed the RSC annual guideline.
4. Pregnancy and breast feeding.
5. Positive HIV test.
6. A history of significant brain disease.
7. Cannot lie on your back for long periods since the pictures will be taken for about 6 hours during which time you will have to lie still on the scanner bed.
8. consumed alcohol within 48 hours before the PET scan

PROCEDURES

This study requires that you come to the NIH as an outpatient for two procedures that will require 3 visits: EVALUATION, PET, and the laboratory tests ~24 h after PET scan. The EVALUATION will be performed first under another protocol (01-M-0254), but the order of the PET visit may be interchanged, depending upon the availability of the instruments.

1) EVALUATION. During the evaluation visit, you will have a history and physical examination. The laboratory tests will include blood and a urine sample for illegal and addictive drugs. The history will include a detailed question on your psychological health. The EVALUATION will take approximately 3 hours.

2) PET Scan: If results obtained during your initial visit show that you are a suitable candidate for this study, you will be asked to return to NIH a second time for the PET scanning procedure. On the day of the PET scan, you will go to the Clinical PET Center where you will be met by a nuclear medicine technologist. You will be shown the scanner used for the procedure and you will have the opportunity to ask any remaining questions. All females will be required to sign and have a pregnancy screening on the day of each PET study before tracer injection. Once you feel comfortable and are ready to continue with the scanning procedure, you will lie down on the scanner bed. To inject the radioactive tracer, and to monitor your blood during the study, one venous catheter will be inserted into one arm. The venous catheter will remain attached to you until the end of the scan.

Just before injection of radioactive tracer, a 20-minute scan (called a “^68Ge transmission” scan) will be performed. This is to provide measures of the body that will help us more precisely calculate the information from the subsequent scans. After the transmission scan is done, the radioactive tracer, \([^{18}F]\)SP203, will be injected into a vein in your arm. We will inject 5 millicuries (a millicurie being a measure of radioactivity) of \([^{18}F]\)SP203, and then we will begin the PET scan. We will perform repeated PET scans from head to upper thigh during which we will ask you to lie still. The scan will produce a "picture" of the distribution of radioactivity in your body. The first scan will take about 100 minutes starting with the injection of the PET tracer. We will do additional four scans, approximately one 1 hour scan every 100 minutes. Therefore, total length of the scans is about five hours. You can come out of the camera between scans.
For the purpose of determining the breakdown of the tracer in the body, we will also draw approximately two tablespoons (30ml) of blood from another vein in your arm one time during this imaging session. We will also ask you to collect all urine during the entire period of the PET scans.

In addition to the procedures described above, we will check monitor your EKG, blood pressure, respiration rate and heart rate during the initial part of the study.

Pictures will be taken for about 4 hours during the 5 hours after injection of \([^{18}\text{F}]SP203\). The first scanning session will last about 2 hours, followed by 30 minute break outside the camera, followed by about one hour in the camera, another 30 minute break, and a final one hour scanning session. During the scans, you will have to lie still on the camera bed. During the breaks, you will be asked to go to the bathroom to void. This will eliminate radioactive urine to minimize your radiation exposure.

You will be asked to return to the Clinical Center for blood and urine tests ~24 h after the PET scan to.

HAZARDS AND PRECAUTIONS

Potential Risks
Potential risks or inconveniences to you associated with this study include: 1) radiation exposure from the PET and transmission scan, 2) PET scanning, 3) Arterial/venous lines placement and blood sampling.

1. Radiation Exposure Risks
You will be asked about any prior research participation involving radiation exposure so that your exposure would not exceed, in combination with the present study, a total effective dose of 5 rem per year, an annual limit established by the NIH Radiation Safety Committee for research studies. This limit does not include radiation exposure received for medical reasons.

This research study involves exposure to radiation from \([^{18}\text{F}]SP203\) and transmission scans. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation you will receive by completing participation in this study is from 5 millicuries from PET scan (a millicurie is a unit of measure of radioactivity) and from a 68Ge transmission scan. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving slightly greater than minimal risk and necessary to obtain the research information desired.

Since this is an exploratory IND compound, the whole-body biodistribution, radiation absorbed dose in human have not been studied yet. Based on animal studies, we estimate that you will receive a total of 2.0 rem to your lungs, 1.1 rem to your kidney, and 1.01 rem to your brain. All other organs will receive smaller amounts of radiation. We estimate that the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 0.6 rem. This calculated value is known as the “effective dose” and is used to relate the dose received by all organs in a single value. The amount of radiation received in this study is within the dose guideline recommended by the NIH Radiation Safety Committee for research subjects. (The guideline is an effective dose of 5 rem per year.)

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth’s air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in one year and two months from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no
harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in your chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is approximately 0.02 percent. Therefore, your total risk of fatal cancer may increase from 25 percent to 25.02 percent. This change in risk is small and cannot be measured directly.

Please tell your doctor if you have been in research studies or received any medical care at the NIH or other places/hospitals that involved the use of radiation so that we can make sure that your total exposure from all studies is not too large. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant, suspect you are pregnant, or breast feeding, you may not participate in this research study. It is best to prevent or avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults. If you are a woman of child bearing potential, you must consent to have a pregnancy test before PET scanning to make sure that you are not pregnant or you may not participate.

2. PET Scanning

PET scanning, a procedure that is performed with the subject lying on the scanner bed, detects injected radioactivity within brain. There are no known physical hazards associated with this procedure. The special mask you will be required to wear during PET scanning is not associated with any danger but may be somewhat uncomfortable. You will have your arms and abdomen wrapped with body-restraining sheets to minimize movement throughout the scan. This may add some additional discomfort or restlessness.

3. Arterial/Venous Line Placement and blood sampling

Arterial catheterization has been shown to be a generally safe and reliable method to obtain arterial blood sample. Placement of a radial arterial catheter may cause bruising or infection. There is also a risk of occlusion and microemboli. In the past, over 3,000 arterial catheters have been placed in the PET department. Of these, two complications requiring physician's care were reported. In the first case, a small radial artery aneurysm developed several months later, which was successfully repaired surgically. In the second case, a radial artery thrombosis developed 28 days later, which was also successfully repaired surgically. The arterial line will be placed by a member of the anesthesiology staff after confirming normal double circulation (both radial and ulnar arteries).

Venous catheter insertion, which is less invasive than arterial catheterization, can also be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize these risks.

Subjects will have no more than 250 mL (about 1 pint) blood sampling including that for lab tests. Careful screening of health status will be done prior to the enrollment in the study. Subjects will be asked not to donate blood for a period of eight weeks after the participation is completed.

Potential Benefits:

There is no direct benefit to you by participating in this study. However, you will receive a thorough medical examination and laboratory screening.
Payment:

You will be paid for your participation according to standard NIH payment schedules. You will be paid $50 for completing the initial assessment visit, $310-320 for the full second day of PET scanning, and $40 for the final day of blood and urine analysis.

We thank you for taking the time to read this consent form, and for your interest in this study. Please let us know if you have any questions regarding this project.

Confidentiality

Personal information will be stored using a confidential case number, and no identifiers (name, address, phone number, etc.) will be used that could allow direct linking of database information to individual subjects. Where temporary linking of information with identifiers is needed, such identifiers will be temporarily attached to the data, and will be removed after information has been encoded.

Withdrawal from Study

You can voluntarily withdraw from the participation in this study at any time, including during scanning procedures, if you wish to do so. We may also decide to end your participation in this study if unexpected situations arise that indicate it is necessary to do so.

HIV Testing

As part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of your fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.
2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.
3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.
4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of
1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.

a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.

b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.

c. The Clinical Center may report certain communicable diseases, including AIDS and symptomatic HIV infection, to appropriate State and Federal government agencies.

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: (301) 496-2381.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.
4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Amira K. Brown Ph.D.; Building 31, Room B2/B34, Telephone: 301-435-1695. Or Robert B. Innis, M.D., Ph.D., Building 31, Room B2/B37, Telephone: 301-594-1089. You may also call the Clinical Center Patient Representative at (301) 496-2626.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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<thead>
<tr>
<th>COMPLETE APPROPRIATE ITEM(S) BELOW:</th>
<th></th>
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<tbody>
<tr>
<td><strong>A. Adult Patient’s Consent</strong></td>
<td><strong>B. Parent’s Permission for Minor Patient.</strong></td>
</tr>
<tr>
<td>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.</td>
<td>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor’s Assent, if applicable.)</td>
</tr>
<tr>
<td>Signature of Adult Patient/Legal Representative Date</td>
<td>Signature of Parent(s)/Guardian Date</td>
</tr>
<tr>
<td><strong>C. Child’s Verbal Assent (If Applicable)</strong></td>
<td></td>
</tr>
<tr>
<td>The information in the above consent was described to my child and my child agrees to participate in the study.</td>
<td></td>
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<tr>
<td>Signature of Parent(s)/Guardian Date</td>
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<tr>
<td><strong>THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE</strong></td>
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<tr>
<td>Signature of Investigator Date</td>
<td>Signature of Witness Date</td>
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