STONY BROOK
STATE UNIVERSITY OF NEW YORK

COMMITTEES ON RESEARCH INVOLVING HUMAN SUBJECTS
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Protocol Summary Form

TITLE: Advancing Personalized Antidepressant Treatment Using PET/MRI
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A. SPECIFIC AIMS:

Despite the burden of failed trials, there are currently no tools for treatment selection in Major Depressive Disorder (MDD). Referring to a recent Positron Emission Tomography (PET) study using 2-[^{18}F]-fluorodeoxyglucose (FDG), NIMH Director Dr. Insel remarked that PET imaging is **"**on the cusp" of aiding in MDD treatment decisions. To finally realize this goal, the limitations of previous FDG studies must be addressed, including limited sample size, lack of placebo comparison (the placebo effect is a significant obstacle to evaluating treatment mechanism and efficacy), and use of relative outcome measures. In the proposed study, FDG imaging before and after Selective Serotonin Reuptake Inhibitor (SSRI) treatment will be performed using a simultaneous PET/Magnetic Resonance (MR) scanner and: (1) the largest sample size to date; (2) a placebo group; and (3) full quantification using analysis of FDG activity in plasma, which yields more accurate estimates of metabolism than relative activity.

Aim 1: Determine a Pretreatment Marker of SSRI Effectiveness Using PET. With the goal of reducing MDD burden, many studies have assessed the utility of FDG-PET in antidepressant treatment prediction. However, due to the limitations listed above, there is no consensus on which brain regions are predictive of treatment efficacy. In addition to serving as a biomarker of SSRI effectiveness, only conclusive determination of these regions will provide insight into depression pathophysiology, helping uncover SSRI mechanism of action, and aiding in the search of novel therapeutics. Based on our preliminary data and other, similar studies, we hypothesize that SSRI-induced change in the Hamilton Depression Rating Scale (ΔHDRS) will be correlated with pretreatment metabolic rate of glucose (MRGlu, quantified using arterial blood analysis) in three potential regions: (1) midbrain, (2) right anterior insula, and/or (3) left ventral prefrontal cortex.

Aim 2: Isolate the Neurobiological Basis of the "Loss" Research Domain Criteria (RDoc) and the Change Associated with Treatment. Using a factor analysis of the HDRS, we have previously demonstrated that the "loss" RDoC criteria is significantly correlated to MRGlu in frontal cortical areas. We therefore hypothesize that change in MRGlu (pre to post treatment) in these regions will be correlated with symptom improvement specifically in "loss" symptoms. As an exploratory extension, we will determine whether these changes are treatment-specific (i.e. to SSRI or placebo). A validation of our hypothesis suggests a targeted mechanism of action, and provides

a significant step forward for precision treatment. If regional changes in MRGlu are not correlated to improvement in this RDoC category, it suggests that SSRI (or placebo) induced changes may be a downstream effect that should be examined further.

Aim 3: Validate NonInvasive Full Quantification of MRGlu Using Simultaneous Estimation. Full quantification of brain MRGlu with FDG (as performed in this study) requires measuring FDG in arterial plasma (input function) from arterial catheter insertion and blood analysis. This costly and invasive procedure creates a barrier to widespread PET use. Our group has developed an innovative method for Simultaneous Estimation (SimE) of input information and PET outcome measures (e.g., MRGlu). SimE fully quantifies brain MRGlu without requiring an arterial catheter. In the case of FDG, our data suggests that SimE used with a single venous sample can provide accurate results. We further hypothesize that the venous sample may be entirely replaced by study data (e.g., injected dose) and biometrics (e.g., body surface area, lean body mass index). Using two different approaches (statistical imputation and physiological parametric modeling) and previously collected data, we will train the SimE for accurate quantification in the absence of blood data. The rich data collected in this study will then provide a robust benchmark for validation of the SimE approach.

B. BACKGROUND AND SIGNIFICANCE:

Despite current medications, morbidity and mortality of Major Depressive Disorder (MDD) remain high. (Benton, Staab et al. 2007) According to the World Health Organization, MDD affects 121 million people worldwide, and is projected to be the second leading cause of global disability by 2020. Monotherapy with SSRIs is the most widely used treatment for MDD.(Leuchter, Lesser et al. 2008) However, on average, SSRIs require six weeks for onset of action, and two-thirds of those on SSRIs fail to achieve remission.(Trivedi, Rush et al. 2006, Leuchter, Cook et al. 2010) Compounding this problem, patients with residual symptoms are significantly more likely to discontinue treatment or relapse, be hospitalized for medical and psychiatric conditions, or die of suicide and other causes.(Trivedi 2003, Trivedi, Rush et al. 2006, Warden, Trivedi et al. 2007) Although eliminating ineffective treatment trials would significantly reduce patient suffering and healthcare costs, (Taylor, Youngblood et al. 2005, Leuchter, Cook et al. 2010) clinicians currently do not have the tools to objectively select treatment based on an individual's likelihood of remission. Therefore, there is an urgent need to identify markers predictive of an individual's SSRI treatment outcome (Taylor, Youngblood et al. 2005, Leuchter, Cook et al. 2010). Developing this personalized treatment requires increased understanding of the relationship between pretreatment neurobiology, SSRI-induced biological changes, and the corresponding symptom improvements.

Our proposed study, in which FDG-PET scans are acquired before and after escitalopram (or placebo) treatment, avoids these previous limitations by standardizing treatment across all subjects, enrolling 120 subjects to ensure that at least 100 will complete the protocol (largest sample size to date), performing full quantification with arterial blood sampling, and a priori defining the clinical outcome measure as ΔHRDS. Further, we will uncover neurobiological correlates of pathophysiology that span diagnoses.

Potential Noninvasive Estimation: PET research/clinical laboratories have differing levels of software and/or hardware expertise. The key, therefore, to promoting widespread PET use is to develop multiple, validated pathways for noninvasive imaging. In this study, we will evaluate Simultaneous Estimation.

Simultaneous Estimation (SimE) Algorithm. Traditional FDG estimation approaches require measurement of both the arterial input function and PET brain signal to quantify MRGlu. In contrast, SimE takes advantage of the fact that each brain region shares the same input function. As such, SimE can quantify the input function and MRGlu at the same time using only the PET

brain tissue signal (from multiple brain regions) and one blood sample. This is possible under minimal assumptions, but requires sophisticated data processing. SimE assumes a parametric model to describe the common input function, and incorporates this model's free parameters together with the free parameters related to MRGlu into a cost function that is optimized during the estimation process. SimE has been thoroughly tested on simulated data.

Optimization strategy for SimE and Clustering. Compared to traditional analysis, SimE increases the number of free parameters that need to be estimated and therefore the computational complexity of the optimization. Standard non-linear regression techniques, such as those based on the Newton-Raphson algorithm, are not always suitable for this complex optimization. Currently, SimE is implemented with a robust optimization algorithm known as simulated annealing. This technique takes its name from the analogy of annealing two materials by heating them to a high temperature and then cooling them slowly. The parameters identify the state of the system and the cost function to be minimized is the energy of the state. The algorithm travels iteratively through the parameters' space by randomly choosing a new set of parameters at each step. At each step, the new set of parameters is accepted with a probability related to the decrease in the cost function (energy) that is associated with the new state.

The kinetic richness of the brain regions that are simultaneously estimated can greatly affect the simulated annealing performance. Including regions with similar kinetics only increases the cost function dimensionality, without adding useful information. With FDG, we have optimized the performance of SimE through the development of a data-driven voxel-based algorithm that automatically determines five subject-specific regions (via k-means clustering of grey and white matter voxels) for use with the SimE approach.

Simultaneous Estimation Anchor: SimE has been recognized as a promising approach for noninvasive PET, as it works for several tracers used in neuroreceptor studies. By itself, however, SimE does not obviate the need to draw blood during the scan. To ensure model identifiability, at least one blood sample must be taken and used as an individual. We hope to be able to eliminate this single blood draw, which would help reduce barriers to widespread PET use.

C. RESEARCH DESIGN AND METHODS

1. Research Site

The PET/MRI scans will be performed at the Imaging Center (Ambulatory Care Pavilion) at the Stony Brook University Hospital.

2. Study sample

N = 120 (diagnosed with MDD) will be enrolled to obtain 100 subjects who complete the protocol
Age range: 18 years and above.

We anticipate the sample will comprise approximately equal numbers of males and females. No ethnic/racial/gender group is excluded.

3. Recruitment Methods

1. Advertisements (flyers, brochures): Subjects will be recruited through response to advertisements, including local newspapers, on Craigslist and other websites. Approved fliers will be distributed around Stony Brook campus, other campuses, off campus locations such as health fairs and places of worship (with permission), and via letters from OPD to patients on their waitlist. Texts of advertisements and other materials to be distributed in recruitment efforts will be submitted to the IRB for approval before they are prepared for distribution. The use of websites and newspapers will allow us to target a

broader range of the population.

2. Subjects will be recruited through lists obtained from the electronic medical record and provided to the study team by Research Services. The information we will receive for each patient include: MRN, patient age, name of treating physicians/nurses, date of most recent encounters, prescribed medication, diagnostic code with its corresponding official description and a free text description. Our study coordinators and clinician will have access to the data. Our team would contact the treating physician of potential participants through letter or telephone call. We will then ask the treating physician to provide information about our study to the patient, or ask the patient if we may contact him or her with more information.

3. Subjects will be recruited through ResearchMatch.org. Potential volunteers will be sent a message through the website providing a brief overview of the study and inclusion criteria. This message will use language that is IRB approved. Volunteers will be able to respond to the message with "Yes, I'm interested" or "No, thanks". If the subject is interested, Research Match will release their contact information to us and they will be contacted by our study team for screening and recruitment.

4. Screening

Patients will first be screened by phone, then in person. All patients will be assessed clinically through history, Structured Clinical Interview for DSM IV (SCID I, though additional questions may be added for consistency with DSM-5), Montgomery–Åsberg Depression Rating Scale (MADRS), review of systems, self-report measures, physical examination, routine blood (~15 ml) for thyroid function and pregnancy tests. Patients may be video or audio-recorded with their consent during the administration of these scales.

INCLUSION CRITERIA	Determined by:
(1) Age range 18 years and above	Interview
(2) Capacity to consent	Interview
(3) Diagnosis of MDD and suffering from a major depressive episode	Interview; SCID-5
(4) Score of at least 22 on the MADRS	MADRS
EXCLUSION CRITERIA	Determined by:
(1) Significant active physical illness, particularly those that may affect the brain and use or start of medication during the study that will significantly affect study results	Interview; clinician judgment
(2) Need for use of medication during the study that will interact with the study medication. Need to start medication that will affect study results (anti-epileptics, antidepressants, beta blockers, medications with serotonergic or GABAergic modes of action)	Interview; study clinician
(3) Patients considered at significant risk for suicide	SCID-5; Interview
(4) Patient is unlikely to be able to tolerate medication washout, or the ~3 week interval (5 for fluoxetine) following washout (drug free period). Medication washouts will be supervised by a study physician or nurse.	Interview

(5) For females: Pregnancy, currently lactating; planning to conceive during the course of study participation, or abortion in the past two months.	Interview; HCG urine
(6) Coumadin treatment within 10 days of PET scanning	Medical history
(7) Any MRI contraindications, including metal implants, pacemaker, metal prostheses, orthodontic appliances, or presence of shrapnel that are contraindicated for MRI.	Medical History; Interview
(8) Bipolar Disorder	SCID-5; Interview
(9) Current psychosis	SCID-5; Interview
(10) High potential for excessive drug/alcohol use during the treatment period (excluding nicotine or cannabis)	SCID-5; Interview
(11) Currently taking effective antidepressant	Interview
(12) Prior treatment in current episode with escitalopram (ESC) for ≥ 4 weeks taking ≥ ⅔ PDR maximal dose	Interview
(13) Prior intolerance of escitalopram (ESC)	Interview
(14) Significant neurological deficits.	Clinical interview, Trails B, and medical history
(15) ECT within the past 6 months	Interview

* Subjects will be eligible if the injected dose and dosimetry of the radiotracer are known and the cumulative annual exposure of the previous study and this study is lower than the annual limit for research subjects defined by the FDA (see below).

D. PROCEDURES

Participants will have a PET/MRI prior to and following 8 weeks of SSRI treatment (escitalopram) or placebo. The initial PET/MRI will be completed after up to a 4-week washout period. Once the washout is complete, subjects will remain off medication for approximately three weeks prior to the first scan (and initiation of treatment). Patients who are unable to tolerate this washout and drug-free period will be removed from the study. They will be monitored with the CGI during this period and have weekly contact with the clinician during washout. After the washout, the rater will administer scales such as the MADRS, HDRS, and CGI.

PET/MRI procedures will be performed utilizing the Siemens Biograph mMR-System located at the Ambulatory Care Pavilion. Participants will complete a metal screening form prior to the procedure to ensure there are no MRI contraindications (e.g., pacemaker, non-MR safe metal implants). Participants will be given a list of guidelines before the day of the PET/MRI scan. A pregnancy test will be performed on the day of the scan for female participants to confirm that pregnancy has not occurred.

Preparation of the subject will include the placement of venous lines (for radiotracer injection and blood sampling), and an arterial line (for blood sampling only). At the time of injection, blood sampling will be initiated. 128 mL or less (about 4 ounces or 1/2 cup) will be collected during each scan. Approximately 8 ml of this will be drawn for assays of candidate gene expression and polymorphisms. If the second IV or the arterial line cannot be placed for any reason, we will continue the scan without them using the Simultaneous Estimation Anchor for data analysis. (If the arterial line is not used in the baseline scan it will likely not be used in the follow-up scan for consistency.)

An MRI scan will be performed simultaneously. This will include various structural (e.g., T1- and T2-weighted images, diffusion tensor imaging [DTI]) and/or functional (e.g., pseudo-continuous arterial spin labeling [pcASL]), pulse sequences. Psychological tasks will not be conducted while the subject is in the scanner. However, a resting state fMRI may be performed. Participants will be given a list of post arterial line instructions at the end of the scan.

The PET/MRI procedure will take approximately 1 hour. Before or after the scan, subjects maybe asked to place their leg in the scanner for a quick (<10 min) MRI acquisition. Following the initial PET/MRI, the study treatment visits will be weekly for 4 weeks and then biweekly for 4-8 weeks (4 weeks for placebo subjects and 8 weeks for the escitalopram subjects). However, in the case that patients cannot make an appointment, the study team will accommodate the patients' schedules. The nurse practitioner will be seeing subjects in her office in the Health Sciences Center. In case of emergency, the nurse practitioner will escort the subject to CPEP. The target treatment duration will be 12 weeks, for those on SSRIs. (For this reason, the blind will be broken at week 8.) At each visit, the clinician will complete assessments such as the HDRS and CGI. (Participants who have not attained remission at Week 12, but have HDRS17 ≤ 10, will have another optional visit at week 14 to allow a participant close to remission an opportunity to achieve it.) Patients will be randomized to either: 10mg ESC for one week, 20mg for two weeks and 30mg thereafter or placebo. The subjects will be randomized by the pharmacy, keeping the researchers blinded. This may be modified based on clinical judgment. After 8 weeks of treatment, the participant will have another PET/MRI that will follow the same procedures as the first PET/MRI.

For participants using substances (including nicotine, alcohol, prescribed medications, or other medications), we will monitor the times/amounts of substance taken throughout the study by self-report. When possible, substance use will be halted two half-lives before the PET/MRI scan. When that is not possible or will significantly affect the comfort of the subject, baseline and post-treatment PET/MRI scans will be scheduled at similar times relative to substance administration in order to minimize the effects of the substance.

When possible, participants will also have follow-up visits at 6 and 12 months after the start of the treatment period. Subjects in the treatment group will be removed from the protocol and clinically treated if their depression worsens or they respond inadequately to the drug. After the study, subjects in both groups will be given referrals for continuing treatment elsewhere.

To reduce the burden of the patients on placebo, the placebo trial will have a target of 8 weeks. (For this reason, all subjects will receive PET/MRI scanning at week 8.) Recent studies have indicated that response to placebo, if it has not occurred by week 8, is unlikely to occur24, 25, 26. To provide an opportunity for placebo non-responders to receive active drug and to aid in recruitment, we will provide 8-12 weeks of SSRI treatment to placebo non-responders. Note, this will also provide additional rich study data as these subjects will have received a PET/MRI prior to both their placebo and SSRI treatment. This 8–12 week treatment period will follow the same procedures as those who were assigned to the escitalopram treatment, including visits with the study psychiatrist or psychiatric nurse practitioner and psychologist and similar data collection procedures. Frequency of visits may be determined at the clinician's discretion. To standardize protocols, we continue (or begin, in the case of those receive placebo) ESC treatment after the second PET/MRI. However, if the subject does not respond or worsens on ESC, we will change treatment as medically indicated.

Cognitive Function: When possible, participants will complete a battery of tasks (30 min) on the same days as the PET/MRI to measure cognitive functions relevant to mood symptoms and hippocampal structure and function, including measures of declarative memory, stimulus-response/reward learning and executive function. As a function of the design of the trial, cognitive

data will be captured while participants are in either depressed or euthymic mood states.

During the protocol, we aim to have study subjects meet/speak to the same study coordinator and clinician consistently. However, due to scheduling constraints, other trained personnel may meet with or contact the study participant in the course of the protocol. In addition, due to the complexity of the study, participants will be in contact with trained personnel not named in this protocol (e.g., the MRI technician and back up technician, PET suite nurses and nuclear technicians). All such personnel are trained for the function they perform in the study.

Image Processing: After MRI and PET processing is performed, the data will be processed using the semi-automated analysis pipeline developed in CUBIT. MRI processing includes segmentation (grey, white, csf) and parcellation into different regions of interest. PET processing includes motion correction, coregistration to the MRI, determination of regional activity over time (time activity curves) and modeling of the time activity curves. The modeling requires information about the radioactivity of plasma during the scan. These techniques have been previously described. (Parsey, Ogden et al. 2010, Miller, Hesselgrave et al. 2013) Using this analysis, the metabolic rate of glucose (MRGlu) can be calculated. The arterial input function (as well as Simultaneous Estimation, for comparison) will be used to derive the regional MRGlu.

E. STATISTICS

Aim 1: Correlation between HDRS and pretreatment MRglu will be determined in the ESC and placebo treatment groups in the three specified regions. In post hoc analysis, spatial resolution will be improved through examination of correlation between whole brain voxel MRglu and HDRS using SPM8 on aligned voxel based parametric images. Our group has extensive experience performing these analyses. For both analyses, outcome possibilities include: differential treatment ΔHDRS prediction (i.e. significant correlation, with different sign for placebo and ESC; significant correlation, within different regions, for placebo and ESC; significant correlation for one treatment only); ΔHDRS prediction insensitive to treatment (i.e. significant correlation in same region, same direction); or insignificant correlation with HDRS for both treatments. The former outcomes would be immediately clinically significant and applicable. The final option, though unlikely based on preliminary data, would also be an important finding and suggest that, either the cohort should be expanded, or additional imaging/clinical measures are needed for prediction.

The power analysis was performed with an estimated 50 subjects per treatment. With a cohort of 50 subjects (on SSRIs), we can detect a true correlation as low as 0.39, with 80% power (two-tailed analysis, Δ= 0.05). In our FDG treatment study, the observed R2 value was 0.32, meaning the true correlation between the data was 0.57 (significantly higher than 0.39). However, this is almost certainly an overestimation because only the voxel cluster highly correlated to the outcome was chosen (as in all cited studies).

Aim 2: The change in MRgIu from pre to post treatment (SSRI and placebo) will be calculated in the midbrain cluster defined by our preliminary studies. The correlation between this value and ΔHDRS will be assessed with both SSRI and placebo groups as well as with separate cohorts, to determine if there is an effect of treatment. As with Aim 1, a post hoc analysis will also be performed examining this correlation over all voxels.

Power Analysis. The partial correlation for each cluster and the factor related to “loss” varies between 0.5 and 0.6, meaning the true correlation ranges between 0.71 and 0.77. Based on this, using a single cohort (n=50), a true correlation as low as 0.39 can be detected with 80% power (two-tailed analysis, Δ =0.05).

When cohorts are combined (n=100 completers, of 120 enrollees), a correlation as low as 0.27 can be detected.

Aim 3: In a previous cohort, we investigated SimE performance with FDG (and four other tracers). The optimal timing for the blood sample used to anchor the FDG SimE estimation was found to be 40 minutes after injection. At this time, FDG venous and arterial samples are essentially interchangeable. Results using this 40-minute blood-based anchor show that SimE-derived MRGlu are close to MRGlu derived using arterial sampling-based estimation: slope 0.730, correlation 0.955 with compartmental analysis slope 0.876, correlation 0.974 with Patlak analysis. Validation: Validation will be considered complete when MRGlu using conventional (Patlak) analysis and arterial samples matches MRGlu calculated with SimE and one venous sample in the proposed study data. The threshold will be a correlation of at least 0.95 and slope of 0.85 in at least 30 subjects.

F. FUNDING STATUS

This study will be funded through the National Institute of Mental Health (R01MH104512-01A1; 1123782-1-70976), the DANA Foundation (Coeus Proposal #20458, PN15125265; 1128493-1-73073), the Brain and Behavior Research Foundation, (Grant #24459; 1134680-1-75849), internal funding from the Department of Computer Science and pilot funding provided by the Department of Radiology for PET/MRI scan costs.

G. DATA and SAFETY MONITORING PLAN (for more than minimal risk studies)

Access to research data will be allowed only to members of the research team or institutional personnel as part of a routine audit. Records may be reviewed by state or federal regulatory agencies and their personnel. Research records, like other medical and clinical records, will be kept confidential to the extent permitted by law. There are legal advocacy organizations that have the authority under state law to access otherwise confidential subject records, though they cannot disclose this information without the subject's consent. All hard copies of records are kept in locked files. Coded computer files will be stored in a database which is password protected and behind an institute and department firewall.

The Data Safety Monitoring Board (DSMB), consisting of the study physician (Manu), psychologist (Perlman) and a member external to the study (e.g., Dr. Kenneth Gadow, Professor of Psychiatry and Director of Clinical Research, Cody Center for Developmental Disabilities) reviews study procedures, subject progress, and imaging data to ensure the safety of participants and the validity and integrity of the data.

Study protocol(s) and consent form(s) were reviewed by the DSMB prior to project initiation. The DSMB also established operating procedures for reviewing patient safety data and source data generated from this study. This includes regular meetings of the DSMB. DSMB recommendations will be shared with the PI (or IRB as necessary) following the meeting. DSMB members will be able to reach each other (or the IRB) in between meetings by phone or e-mail.

IRB protocols and informed consent documents will be reviewed annually by the Stony Brook University IRB. In addition, any serious adverse events (SAE) will be addressed and reported to the IRB and DSMB within 48 hours. An SAE is defined as follows: death, life-threatening adverse event, an unexpected event requiring unplanned inpatient hospitalization, persistent or significant disability/incapacity, and medically significant event.

The PI will also be responsible for reporting any SAEs to the NIMH program officer. Actions taken by the local IRB in response to adverse event reports will be reported to the NIMH Project Officer

and the Office of Research Compliance.

Based on its review of the study procedures, subject progress, and imaging data, the DSMB has the authority to prevent the study from starting or to stop the study after it has started.

Once a patient enrolls in the project, they are given a code number, which is used for all subsequent computer data and/or lab forms. The code list and patient names as well as all data are kept in locked files in locked offices with access limited to those directly responsible for maintenance of these files by the research team. Subjects whose history is obtained through the collection of family history information (from the interviewee) are also considered research subjects. They are subjected to minimal risk because all information is confidential. There are procedures to safeguard confidentiality of the information gathered about them from other family members, including names or identifying information kept on the family history form or in the records. All hard copies of records are kept in locked files. Computer files will be stored in a database which is password protected. The database is stored on a secured server. Only essential staff will be allowed access to this information. The study could not be completed without this information.

Blood samples for genetic testing will be de-identified and coded only with a number; no personally identifying or clinical information will be stored with the samples or provided to testing laboratories.

The physician or nurse practitioner will complete a CGI for all subjects weekly for the first 4 weeks and then weekly or biweekly thereafter. They will be assessed for suicidality or worsening of depression. If this is the case, the subject will be dropped from the study and be treated clinically immediately.

Side effects will be monitored in standard clinical fashion. The physician or nurse practitioner will interview patients about possible side effects at each contact and patients will be encouraged to call with any questions that may arise at any time. Response to side effects will depend on the circumstance. Doses may be titrated or patients may have medication discontinued, if clinically indicated.

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