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Translational Neuroscience Optimization of GlyT1 Inhibitor

Project Description
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Purpose: Schizophrenia is one of the leading causes of disability, principally because current treatments lack substantial efficacy for treating cognitive impairments associated with schizophrenia (CIAS). Deficits in *N*-methyl-D-aspartate (NMDA) function are thought to contribute to CIAS by interfering with the integrity of brain functional connectivity and neuroplasticity. Enhancing NMDA receptor function via the glycine site may reduce cognitive deficits. Glycine transporter-1 inhibitors (GlyT1Is) act by raising synaptic glycine levels and increasing glycine occupancy of the high-affinity ($glycine_B$) coagonist site of NMDA-receptor (NMDA-R) thus enhancing NMDA-R function. However, with higher doses of Glyt1Is there is a plateauing and/or worsening of effects suggestive of an inverted 'U' dose response regulation of NMDA-R function. This study is designed to test the efficacy of two doses of active PF-03463275 (40 mg, 60 mg) versus placebo in combination with cognitive remediation (CR) for the treatment of CIAS.

Aims:

- Aim #1:To test the efficacy of treatment with two doses of PF-03463275 (40 mg or 60 mg versus placebo) combined with CR to enhance cognitive function in chronic, stable, antipsychotic treated patients with schizophrenia as measured by the composite score on the MATRICS Consensus Cognitive Battery (MCCB).
- Aim #2: To test the efficacy of treatment of 40mg or 60mg controlled release PF-03463275 BID combined with Cognitive Remediation (CR) in reducing the deficits in LTP observed in schizophrenia.

Background: Schizophrenia is a chronic debilitating illness with a prevalence of approximately 1% in the general population worldwide, affecting over 3.0 million individuals in the US. The World Health Organization's Global Burden of Disease 2000 ranked schizophrenia as the fifth leading cause of years lived with a disability. Cognitive deficits, for which there are currently no proven treatments, contribute significantly to disability associated with schizophrenia. *As stated by Thomas Insel, there is an urgent need to develop effective treatments for cognitive impairments of schizophrenia (CIAS)* (6). The purpose of the current project is to employ translational neuroscience approaches to optimally evaluate the efficacy of the glycine transporter-1 inhibitor (GlyT1I), PF-03463275, that has not been fully tested and to thereby demonstrate its potential for efficacy in treating CIAS.

Computerized Cognitive Remediation is associated with improvement in cognitive test performance in schizophrenia patients: We (Johannesen, NCT00923078) have completed testing of 24 chronic schizophrenia patients in an in-progress computer-based CR study targeting auditory and visual processing. This 8-week study uses a cross-over design with randomization to training of one modality for 4 weeks, and crossing to the alternate modality for a second 4 weeks. Figure 6 shows effect-size (Cohen's d) comparisons across MATRICS cognitive tests from baseline to the first 4-week follow-up. Small to medium effect-sizes were observed across most cognitive domains in subjects receiving visual training (InSight), exceeding published practice effects (5) on MATRICS tests as well as effects of the auditory training (Brain Fitness) condition on all measures with the exception of NAB Mazes, BVMT, and WMS-III Spatial Span. These effects were obtained using the same visual training software (InSight, Posit Science) and training intensity (5 sessions/week x 4 weeks) as the trial proposed in the current application, therefore, we are confident that our design will have the same efficacy in those receiving CR + placebo and predict enhanced efficacy in the CR + active GlyT1I condition. Retention and training compliance have been excellent with 100% follow-up and subjects completing 96%, on average, of all scheduled InSight training sessions using the incentive payment schedule described in this application.

Human visual cortex neuroplasticity (LTP) is a biomarker of NMDA-R dependent neuroplasticity: As reported by Cavus et al, 2012, (13) data collected on a small sample of subjects in our laboratory show the expected post- stimulation enhancement of N100 ERP amplitude in healthy (aged 51, 34, 27) but not schizophrenia (aged 56, 32, 24) subjects (Fig. 7).

Treatment with the combination of Cognitive Remediation and Glycine Site agonist in schizophrenia patients is both safe and feasible: In a POC study, we (D'Souza et al) have demonstrated the feasibility and safety of combining pharmacotherapy with CR in patients with schizophrenia. Chronic, stable, antipsychotic treated

patients (n=104) with schizophrenia received the glycine site agonist D-Serine or placebo and CR for 12 weeks in a double-blind randomized manner. Both interventions were well tolerated with a ~90 % completion rate (62). These results demonstrate our capacity to successfully recruit, engage and retain sufficient patients as proposed in this study, and also demonstrate the feasibility of combining pharmacotherapy with CR.

Significance: Schizophrenia has been ranked by the World Health Organization's Global Burden of Disease 2000 as the fifth leading cause of years lived with a disability. CIAS affect most patients with schizophrenia (52), precede the onset of illness, range from moderate to severe (53), are strongly correlated with functional outcome (54, 55) and predict disability and vocational functioning better than positive symptoms (55). While the available antipsychotic treatments address the positive symptoms of the disorder, they do not reduce cognitive deficits. In fact, there are no approved treatments for the cognitive deficits of schizophrenia. In summary, developing effective treatments for the cognitive deficits of schizophrenia will represent a significant step forward in the treatment of this major disorder

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1) Males or females 20 to 65 years of age (inclusive).
2) DSM-IV schizophrenia or schizoaffective disorder
3) Ongoing treatment with an antipsychotic except clozapine.
4) No changes in antipsychotics for at least 3 months.
5) No psychiatric hospitalizations for the past 3 months.
6) Genotyped to be CYP2D6 extensive metabolizer genotype.
7) Able to provide written informed consent.

Exclusion Criteria:

1) Female subjects who are pregnant/ breastfeeding or unwilling to practice established effective contraception as determined by the investigator prior to entering the study until 30 days following the last dose of the study. Acceptable contraceptive methods for female subjects include: Double barrier contraception or a combination of a barrier contraception *and* a hormonal implant, injectable, combined oral contraceptive, or male partner who has had a vasectomy; IUD or tubal ligation.
2) Genotyped to be CYP2D6 poor, intermediate, or ultra-rapid metabolizers.
3) Current or past clinically significant or unstable medical illness (per P.I. discretion)
4) Current or past history of significant neurological disorder, including head trauma with loss of consciousness, history of stroke, Parkinson's disease, epilepsy disorder, conditions that lower seizure threshold, seizures of any etiology (including substance or drug withdrawal), those who were taking medications to control seizures, or those who had increased risk of seizures.
5) Evidence or history of significant hepatic disorder, including acute or chronic hepatitis B and acute hepatitis C
6) HIV+ or AIDS.
7) Any condition possibly affecting drug absorption (e.g. gastrectomy).
8) Positive urine drug screen for substances of abuse
9) Treatment with an investigational drug within 30 days or 5 half-lives preceding the first dose of study medication.
10) Clinically significant ECG abnormality (e.g., QTC interval > 450).
11) Concomitant treatment with medications that interfere with cognitive testing (e.g., benzodiazepine) within 12 hours before cognitive testing and cognitive remediation.
12) Concomitant treatment with drugs or foods that are known to interfere with the function of CYP2D6 and CYP3A4.
13) Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2 times the upper limit of normal (ULN) at the screening visit.
14) Current DSM-IV Axis I diagnosis other than schizophrenia or schizoaffective disorder.
15) DSM-IV defined psychoactive substance dependence within 6 months of screening or substance abuse (excluding nicotine and caffeine) within 3 months prior to screening.
16) IQ less than or equal to 70, as determined by the Weschler Test of Adult Reading (WTAR)

17) Treatment with clozapine, lamotrigine or carbamazepine because these drugs may interfere with the effect of PF-03463275 on facilitating NMDA-R function.
18) Treatment with monoamine oxidase inhibitors within 60 days prior to screening.
19) Treatment of refractory schizophrenia.
20) Blood donation within eight weeks of the start of the study.

Recruitment: Subjects for both phases of this study will be recruited by advertisements in newspapers and websites such as Craigslist and flyers that will be posted at various locations at VACHS, by referral from providers and word of mouth. All advertisements and flyers will be reviewed and approved before use by the Human Subjects Subcommittee at the VACHS and the Human Investigations Committee at Yale. In the event that a subject responds to an advertisement, they will be contacting study staff. Subjects who contact the clinic will be invited in for a face-to-face meeting. Furthermore, the research team will reach out to local mental health facilities (including the Connecticut Mental Health Center) through "lunch and learns", etc. for patient referrals. A lunch and learn is a meeting that research staff schedule with clinicians and therapists at local mental health facilities where an overview of current research protocols are presented and discussed. In the event that subjects are referred from clinics or mental health facilities, research staff will require that the subjects' clinician contacts the subject first and then refers the subject to the research clinic.

The investigators and study personnel may work with the mental hygiene clinic to conduct pre-screening chart reviews to determine potentially eligible subjects for this study. If a patient diagnosed with schizophrenia or schizoaffective disorder seems eligible, their primary clinician will be approached for a referral for screening. Subjects will not be contacted directly.

Informed Consent: Subjects who may meet entry criteria will be invited to meet with the research staff, who will fully explain details, risks and procedures as outlined in the consent form. To ensure understanding of the study, the subject will be asked questions about the study procedures and the risks associated with participation. This process generally takes about one hour. If it appears that the study subject does not fully understand the study, the Principal Investigator (PI) may decide that the subject is not suitable for participation. If the subject is still interested after all questions have been answered, he/she will be asked to sign the informed consent form. Subjects will be informed that they can decline to participate in the study without penalty and will be given the opportunity to withdraw from the study prior to analysis of their data. A copy of the consent form will be provided to all subjects.

Great care will be taken to ensure that the subject is able to give informed consent. If any concern arises that the study subject did not fully understand the study, the principal investigator may decide that the subject is not suitable for participation. This process will involve careful explanation of the consent form by a member of the research staff and a post- test to ensure understanding of the procedures and risks of the study. The subject will be required to get 75% of all questions and all the asterisked critical questions correct on a consent questionnaire in order to participate.

For patients with schizophrenia, family and/or non-research clinicians will be involved in the process when available. The patient's primary clinician i.e. non-research clinician (if applicable) will be required to assent to patient's participation. This is standard procedure for this clinic with all studies that involve patients.

Research Design: This is a double-blind, placebo-controlled, within subject POC study of stable patients with schizophrenia randomized to either placebo or active PF-03463275 twice daily in addition to their antipsychotic (except clozapine) for 2 dosing periods, each lasting approximately 5 weeks. Subjects will begin treatment with the study medication upon completion of all baseline procedures. The first week of each treatment will represent a lead in period to evaluate the effects of medication alone on LTP and to confirm compliance and tolerability. All subjects will receive cognitive remediation in addition to placebo/active PF-03463275 for approximately 4 weeks each study period.

Per the P.I.'s discretion, up to 14 days may be added to a treatment period to account for extenuating circumstances, such as departmental closures or scheduling conflicts, which would otherwise inhibit completion of a period within the intended 5 weeks per study period (see procedures table, Appendix: Table 1). For the aforementioned reason, if the subject does not successfully complete a study procedure, he or she may be asked to repeat said procedure, a decision that will be made at the discretion of the principal investigator.

Screening: Subjects will first undergo a phone screen to initially determine eligibility. Information collected during the phone screen will only be used in the event that the subject continues to participate in the study. After determining initial eligibility, research staff will provide a brief description of the research and the subject will present to the clinic for the screening procedures described below.

Part I of the screening will consist of consenting and procedures necessary for medical and psychiatric clearance (i.e., SCID, labs, EKG, physical). Part II of the screening process will consist of history verification, and testing (i.e., assessments of intelligence and cognition). However, the procedures may need to be divided differently between screening visits in cases where subjects have limited time to dedicate to the screening appointments. Screening procedures take approximately 8 hours, and may require multiple visits. Once all screening procedures have been collected, research staff as well as the principal investigator will review all relevant information and determine, based on the inclusion and exclusion criteria, if the subject will continue with the remaining study procedures. For those found ineligible, the information collected during the phone screen will be kept, with the permission of the subject.

At the screening session, the following procedures will take place:

1. The subject will receive a full, written explanation of study procedures and sign a consent form. The subject will be required to successfully complete a questionnaire that will help us confirm their understanding the risks of this study before participation. They will be given two attempts and they will be required to answer all questions correctly. Any questions will be answered and a physician or nurse will be available to answer any medical questions.
2. Subjects will receive a detailed evaluation including a medical history and a physical examination.
3. A psychiatric evaluation and a Structured Clinical Interview (SCID) for DSM-IV (non-0patient) for healthy controls will be conducted.
4. Laboratory tests will include urine toxicology and EKG.
5. A 10-mL blood sample will collected at screening for CYP2D6 genotyping into an appropriately labeled plastic EDTA tube. The whole blood will be transported to Joel Gelernter's laboratory for standard CYP2D6 analysis.

6. Intelligence will be measured using the Wechsler Adult Intelligence Scale IV (WAIS-IV) and will be added as a covariate in the neuropsychological data analysis.
7. Handedness will be confirmed via the Edinburgh Handedness Scale
8. Subjects will meet with a study doctor for cognitive assessments.
9. Subjects will be asked to identify a collateral source of information at the beginning of the screening process (explicitly stated in the consent form) and sign a release of information providing us permission to contact the collateral. A family member, significant other, spouse is preferred. We then contact the collateral to elicit any information that might disqualify the subject or suggest risk to the subject. In instances where there are discrepancies between the information provided by the subject and that by the collateral, we usually disqualify subjects.
10. Subjects will be asked to refrain from all illicit drugs, alcohol, caffeine and other medications for 1 week prior to the test days.

Randomization to PF-03463275: Subjects will be randomized to one of two doses of the glycine transporter inhibitor (GlyT1I) PF-03463275 (40 mg or 60 mg) and placebo twice daily in addition to their standing antipsychotic dose for two treatment periods each lasting approximately 5 weeks. Treatment periods will be separated by a washout period lasting approximately 3 weeks. Randomization will be stratified by antipsychotic treatment and screening performance Intelligence Quotient (WTAR estimated FSIQ 71-90 and >91). Other variables of interest e.g., cognitive test performance (MCCB composite score), BDNF genotype, BDNF levels (low, medium and high), antipsychotic dose, that cannot be stratified because of sample size limitations will be examined post-hoc. The dose of PF-03463275 has been determined based upon sub-study 1: doses that produced at least 10% occupancy and attenuation of Ketamine effects on fMRI response to a spatial working memory task will be used in Sub-Study 2.

MCCB: The MCCB (5) consists of 10 tests and provides standard scores and percentiles for each of seven cognitive domains. Domains assessed include: speed of processing, attention/vigilance, working memory (verbal and visual), verbal learning, visual learning, reasoning and problem solving, and social cognition. The MCCB was developed by an expert panel of researchers, under NIMH contract, as a broad yet sensitive

measure to assess cognitive change in treatment studies. The battery includes alternate test forms for repeated administrations. The MCCB will be administered at baseline and follow-ups. Change on the MCCB composite score will be calculated to assess for the overall effect of treatment, with change in specific cognitive domains including verbal and visual learning and short-term/working memory examined as exploratory analyses.

Visual LPT Paradigm: A visual LTP procedure (13, 74) will be administered as a probe of visual cortical neuroplasticity. In brief this paradigm consists of six experimental blocks, each of 2 min duration (Figure 12), administered during electroencephalographic (EEG) recording. The first two blocks serve as baselines, during which subjects complete a visual target detection task. A central fixation cross is replaced by one of two stimuli (Figure 11, panel A) at pseudorandom order with duration of 33ms and average stimulus-onset asynchrony (SOA) of 1216ms (jittered 1075-1340ms); a circular checkerboard (10.5 x 10.5cm, subtending 6^{o} of visual angle) or blue square checkerboard (17.5 x 17.5cm, subtending 10^{o} of visual angle) against a white background. Each block consists of 100 trials, with the circular checkerboard presented 90% (standard) and the blue square checkerboard 10% (target). Subjects are instructed to keep their dominant index finger on a response key button and to respond as quickly as possible to the blue square checkerboard. This target detection task is used to maintain alertness to the visual stimuli and target trials are not included in analysis of LTP. Baseline blocks are followed by a 2-minute period of visual high-frequency stimulation (HFS), in which the circular checkerboard is presented alone at a rate of 8.87Hz (113ms mean stimulus onset asynchrony; 1000 presentations). Subjects are instructed to fix their gaze on the centrally presented “flickering” stimuli and to relax while remaining as still as possible. This rate of high-frequency stimulation is designed to induce potentiation, analogous to the tetanizing stimuli in classic LTP procedures, and produces a prominent ~9Hz visual steady state response over posterior-occipital electrode sites. Subjects are instructed to close their eyes for a 2-minute rest period following high-frequency stimulation to allow visual after-effects to disappear. The rest period is followed by three post-test blocks, identical to the baseline blocks, beginning 2-, 4-, and 18-minutes following stimulation. LTP is characterized by an increase in visual N100 ERP amplitudes evoked by the circular checkerboard stimuli from baseline to post-test blocks.

Risks and Benefits:

1. ***Screening:*** Healthy control subjects (HCS) and schizophrenic subjects (SZS) will undergo a Structured Clinical Interview for DSM-IV conducted by a research assistant and a psychiatric evaluation by the research psychiatrist at the VA Hospital in West Haven. The diagnostic interviews may cover issues, which are stressful to a person, for example, questions regarding the experience of paranoid thoughts or social isolation. Thus, SZS may experience some distress of worsening of psychiatric symptoms.
2. ***Loss of Confidentiality:*** Participation in research may involve a loss of privacy and confidentiality. Therefore, extensive measures are in place to protect the confidentiality of subjects.
3. ***Treatment with PF-03463275:*** In clinical trials in healthy controls and patients with schizophrenia, common risks reported include fatigue, thirst, somnolence, insomnia, headache, akathisia, tremors, nausea, increased urination, gastrointestinal disturbances including abdominal pain, nausea, constipation and diarrhea. Visual disturbances include the brightening of vision and perception of flashing lights and one patient with schizophrenia also reported blurring of vision. These were transient and not associated with any visual changes on further testing. Palpitations, tachycardia and hypotension (in one subject) were noted, but resolved without any medical intervention. One patient with schizophrenia had ventricular systoles and was noted to have a 20 msec increase in QTc interval. Finally, 2 subjects with schizophrenia had elevations in AST/ALT levels and one subject had elevated glucose level attributable to treatment with PF-03463275. Thorough screening and frequent assessments for adverse events (See Section XII) are in place to mitigate the risks. Certain foods and medications may interfere with the metabolism of PF-03463275 and result in very low or high drug levels. This may result in loss of efficacy or increased risk of adverse events. Subjects will be advised to avoid these medications and this will be confirmed at each study visit. These include: Drugs or foods/food products that inhibit CYP2D6 and CYP3A4 (e.g., quinidine, fluoxetine, paroxetine, amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluvoxamine, nefazodone, nelfinavir, ritonavir, troleandomycin, and verapamil, indinavir, itraconazole, ketoconazole, mibefradil, grapefruit and grapefruit juice). Drugs that induce CYP3A4 will also be excluded (for e.g., carbamazepine, phenytoin, phenobarbital, rifampin and rifabutin).

4. ***Long Term Potentiation - Event Related Potentials:*** There are minimal risks associated with EEG/ERP recording. Traditionally, scalp abrasion has been used to improve signal impedance at the electrode site. The EEG/ERP system used in this laboratory is a high-impedance system and does not require scalp abrasion to obtain clean recording. A conductive gel is applied, which can be easily washed out of the subject's hair with warm water. A shower facility for hair washing and sterile linens are available in the laboratory. Electrode caps and sensors will be washed and sterilized between subjects to minimize the risk of transmitting infection.
5. ***Cognitive Remediation:*** There are no known physical risks associated with computer-based cognitive remediation. Fatigue and frustration during training are possible. If this occurs, subjects will be encouraged to take breaks, during which they can drink coffee or halt training for the day. Research staff will monitor subjects during training and may advise them to seek further treatment if symptoms worsen as a result of participation in the study.
    a. *Reduction of Risk:* Subjects will be encouraged to maintain the pace of cognitive exercises and not to be worried about performance. They will be encouraged and reassured. If they need a break, they will be encouraged to take one and return. The cognitive remediation in this study allows for a flexible training schedule. If subjects appear to be getting distressed, they will have the opportunity to talk with one of the investigators and may even be asked to return for the session. At the Learning Based recovery center, Dr. Bell has enormous experience using cognitive remediation in patients with schizophrenia. Overall, this is tolerated very well and subjects usually find it very motivating and helpful. Some of the behavioral questions may be distressing to patients. This risk is discussed in the consent process and subjects will be reminded that they can stop at any time and can choose not to answer. In case of marked worsening of symptoms, they will be evaluated by a psychiatrist, referred to their usual outpatient treater. Further, if indicated they may be escorted to the ER for an evaluation or admission as clinically indicated.

SAFETY

Data and Safety Monitoring Plan: The safety data is reviewed after every test day, during weekly research team meetings, and will be suspended or modified if indicated.
Adverse events will be graded in severity as follows:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4 Life-threatening or disabling adverse event
5 Fatal adverse event

The expected effects of Ketamine will not be recorded as adverse events.
Adverse events > level 3 will be reported to the IRB within 24 hours. Other adverse events will be reported to the IRB in a timely manner, using the following predefined causal relationships:

i. Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
ii. Probable: Adverse event(s) will likely be related to investigational agent(s)
iii. Possible: Adverse event(s) may be related to investigational agent(s)
iv. Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
v. Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Serious, unanticipated and related adverse events will be reported to VA-HSS and Yale HIC.

Informed Consent: Subjects who meet entry criteria mentioned above will be invited to meet with the research staff, who will fully explain risks and procedures as outlined in the consent form. After reviewing this information and answering questions, informed consent will be obtained from all subjects. The informed consent form (see attached), which will be given to the participating subjects, explains all the information pertaining to this study such as the objectives of the study, the procedures, risks and benefits, confidentiality, safety measurements, payment and other aspects of the study. Understanding of the information prior to obtaining consent is verified using a questionnaire (see attached).

Economic Considerations: Sub-study 2:

Sub-study 2Visit	Amount	Method
Screening Visit 1	$25	Cash
Screening Visit 2	$25	Cash
Baseline	$75	Cash
Period 1		
Week 1	$75	Cash
Week 2	$100	Debit Card
Cog Rem-Session 5	$20	Debit Card
Week 3	$100	Debit Card
Cog Rem- Session 10	$30	Debit Card
Week 4	$100	Debit Card
Cog Rem- Session 15	$40	Debit Card
Week 5	$100	Debit Card
Cog Rem- Session 20	$50	Debit Card
Washout Week 1	$20	Debit Card
Washout Week 2	$20	Debit Card
Period 2		
Week 9	$100	Debit Card
Cog Rem- Session 25	$60	Debit Card
Week 10	$100	Debit Card
Cog Rem- Session 30	$70	Debit Card
Week 11	$100	Debit Card
Cog Rem- Session 35	$80	Debit Card
Week 12	$100	Debit Card
Cog Rem- Session 40	$90	Debit Card
Follow- Up	$75	Debit Card

Subjects will be compensated up to $50 for completion of screening processes, which will take place at the VACHS and Yale University. These aforesaid processes will take approximately 8 hours and may take multiple visits. In this case, the total amount of the screening will be split between the visits. For example, the subject will be paid $25 for the first visit and $25 at the subsequent screening.

Subjects can earn up to $1, 555 for completion of all study procedures. Participants will receive compensation only for study visits that are attended. Payments for screening, baseline and week 1 will be made via cash. All other visits will be paid via debit card unless otherwise requested by the subject or his/her conservator, and agreed upon by the P.I.

To encourage participation in cognitive training, additional incentive payments will be dispensed for cognitive training activity, amounting up to $440. Training will be administered over approximately 8 weeks, during which you will be asked to complete approximately 5 sessions per week, for a total of about 40 sessions. Incentive payments will be earned in blocks of 5 sessions, and dispensed according to the schedule outlined in the Economic Considerations Table. A maximum of 5 sessions can be completed each week, and no additional incentive payments will be made after 40 training sessions. A partial payment may be made at the final training session based on the percentage of training you complete toward the next payment point.

In addition to the compensation for each in-person visit, subjects will be compensated $5 for completing each compliance monitoring or CAROMA visit by phone. CAROMA visits will only be completed on weekdays that the research clinic is open. Subjects may earn up to $350 dollars for completing all possible CAROMA visits.

TABLE 1:Substudy 2 Procedures

	Screen	Baseline (2 weeks)		Period 1 (5 weeks)						Washout (3 weeks)		Period 2 (5 Weeks)						Follow - Up
Week	**Screen**	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Day		-14	-7	0	7	14	21	28	35	42	49	56	63	70	77	84	91	98
SCID	x																	
WTAR	x																	
Psych Evaluation	x																	
Physical	x																	
Genotyping	x																	
Randomization				x								x						
PF v Placebo				x	x	x	x	x	x			x	x	x	x	x	x	
CR					x	x	x	x	x				x	x	x	x	x	
PANSS				x		x		x				x		x		x		
SGI				x		x		x	x			x		x		x	x	
PAOFI				x		x		x	x			x		x		x	x	
Movement Exam				x		x		x				x		x		x		
MCCB		x								x								x
LTP				x					x			x					x	
PK				x	x	x	x	x	x			x	x	x	x	x	x	
BDNF				x														
CBC	x			x		x		x				x		x		x		
CMP	x			x		x		x				x		x		x		
ECG	x			x		x		x				x		x		x		
Utox	x	x	x	x		x		x		x	x	x		x		x		

SCID: Structured Clinical Interview for DSM IV; WTAR: Wechsler Test of Adult Reading; CBC: Complete Blood Count; CMP: Comprehensive Metabolic Panel; ECG: Electrocardiogram; Utox: Urine Toxicology screen; CR: Cognitive Remediation; PANSS: Positive and Negative Syndrome Scale; SGI: Sensory Gating Inventory; PAOFI: Patient Assessment of Own Functioning Inventory; LTP: Long Term Potentiation; BDNF: Brain Derived Neurotrophic Factor. Per P.I. discretion, study procedures may be repeated, and the duration of participation may be extended to account for scheduling conflicts and extenuating circumstances. Thus, the number of weeks listed per period may vary.

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