Study Protocol
Biomarker Strategies for Medication-Enhanced Cognitive Training in Schizophrenia
NCT02634684
5R01MH059803-15
Latest IRB approval date: July 9, 2020
IRB expiration date: July 8, 2021

200993

UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

TO: Dr. Neal Swerdlow

RE: Project #200993
Human Psychophysiological Correlates of Sensorimotor Functioning

Dear Dr. Swerdlow:

The above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts. This approval, based on the degree of risk, is for 365 days from the date of **IRB review and approval** unless otherwise stated in this letter. The regulations require that continuing review be conducted on or before the 1-year anniversary date of the IRB approval, even though the research activity may not begin until some time after the IRB has given approval.

The IRB determined that this project presents more than minimal risk to human subjects in that the probability and magnitude of harm or discomfort anticipated in the research are greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Date of IRB review and approval: **07/09/2020**

On behalf of the UCSD Institutional Review Boards,

/js

Kip Kantelo
Director
UCSD Human Research Protections Program
858-246-HRPP (858-246-4777); hrpp@ucsd.edu

Note: IRB approval does not constitute funding **or other institutional required approvals.** Should your studies involve other review committees such as Office of Clinical Trials Administration (OCTA), Office of Coverage Analysis Administration (OCAA), Conflict of Interest (COI), Protocol Review Monitoring Committee (PRMC), and committees under Environmental Health & Safety (EH&S) such as Institutional Biosafety Committee (IBC), Human Exposure Committee (HERC), and RSSC (Radiation Safety and Surveillance Committee), it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens.

If you have questions regarding this correspondence, please contact the "B" analyst who drafted this letter, Joel Stinson, at jstinson@ucsd.edu.

Approval release date: 7/9/2020

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

1. PROJECT TITLE

Human Psychophysiological Correlates of Sensorimotor Functioning

2. PRINCIPAL INVESTIGATOR

Neal R. Swerdlow, M.D., Ph.D., Professor, Psychiatry

3. FACILITIES

Clinical Teaching Facility, UCSD Medical Center, Hillcrest
General Clinical Research Center, UCSD Medical Center, Hillcrest

4. ESTIMATED DURATION OF THE STUDY

7 years from original date of approval

5. LAY LANGUAGE SUMMARY OR SYNOPSIS

These studies assess information processing and neurocognition in clinically normal individuals and in individuals with specific brain disorders. In some cases, studies assess the effects of medications on information processing and neurocognition, either as a means to understand the biological mechanisms that control these processes, or as a way to test the potential clinical value of medications for improving these processes in patients with brain disorders.

6. SPECIFIC AIMS

Certain neuropsychiatric disorders are characterized by a brain-based deficit in the ability to effectively inhibit, or “gate” sensory, cognitive or motor information. To study the physiological basis of this inhibitory deficit, we use prepulse inhibition of the acoustic startle reflex as an operational measure of sensorimotor gating. We study the acoustic startle reflex, including prepulse inhibition (PPI) and prepulse facilitation of startle in neuropsychiatric patients and appropriate control comparison populations.

A substantial literature of preclinical studies demonstrates that prepulse modification of the startle reflex, including PPI, is regulated by specific neurochemical substrates. Among these, brain dopamine (DA) activity is known to regulate PPI via D2-family receptors in portions of the striatum. PPI is disrupted or eliminated in rats by systemic or intracerebral treatment with DA agonists. These and related animal studies have allowed us to identify a specific neural circuitry, connecting limbic cortical structures, through their basal ganglia efferents, to pontine structures, that regulates the amount of sensorimotor gating, as measured by PPI. It would be critically important to determine whether these same substrates regulating PPI in rats, could be extrapolated to humans, and thus allow us to interpret the neural basis for abnormal patterns of PPI in neurologic and psychiatric patients.

In a series of studies, we investigated the neurochemistry of PPI in humans, by documenting changes in PPI in response to specific pharmacologic probes, using adequate sample sizes, agonist-antagonist interactions and informative dose-response profiles where possible. The similarities and differences between the responses to pharmacological manipulations in humans and rats provide important evidence for understanding the neural circuit substrates of PPI in humans.

Differences in sensorimotor gating also distinguish certain groups of normal subjects. For example, lower levels of PPI are found in clinically normal individuals who carry the Val/Val vs. Met/Met alleles for the Val158Met polymorphism of the gene for catechol-O-methyltransferase. In other cases, differences in PPI drug sensitivity distinguish certain groups of normal subjects. For example, amphetamine differentially changes PPI among individuals characterized as having low vs. high novelty seeking personalities. For these reasons, some of our studies interrogate specific genetic and personality characteristics of our test subjects: genotyping is conducted using blood samples, and specific questionnaires are used to evaluate personality and behavioral characteristics of the study populations.

Differences in sensorimotor inhibition will be detected by some, but not other laboratory-based measures, reflecting differences in the particular psychophysical demands of the measure. To add to our

understanding of patterns of sensorimotor inhibition across normal and patient populations, and of changes in sensorimotor inhibition in response to specific manipulations of brain circuitry thought to regulate one form of sensorimotor inhibition (PPI), we also assess Latent Inhibition, Negative Priming, Mismatch Negativity and Gamma Band Synchronization in some of our study groups.

Importantly, measures of sensorimotor gating are associated with higher brain functions, including neurocognitive processes. Thus, in some cases, our subjects complete measures of neurocognition, designed specifically to assess drug effects on processes such as working memory. In this way, we can test the hypothesis that drug-induced increases in sensorimotor gating can contribute to neurocognitive improvements in patients populations.

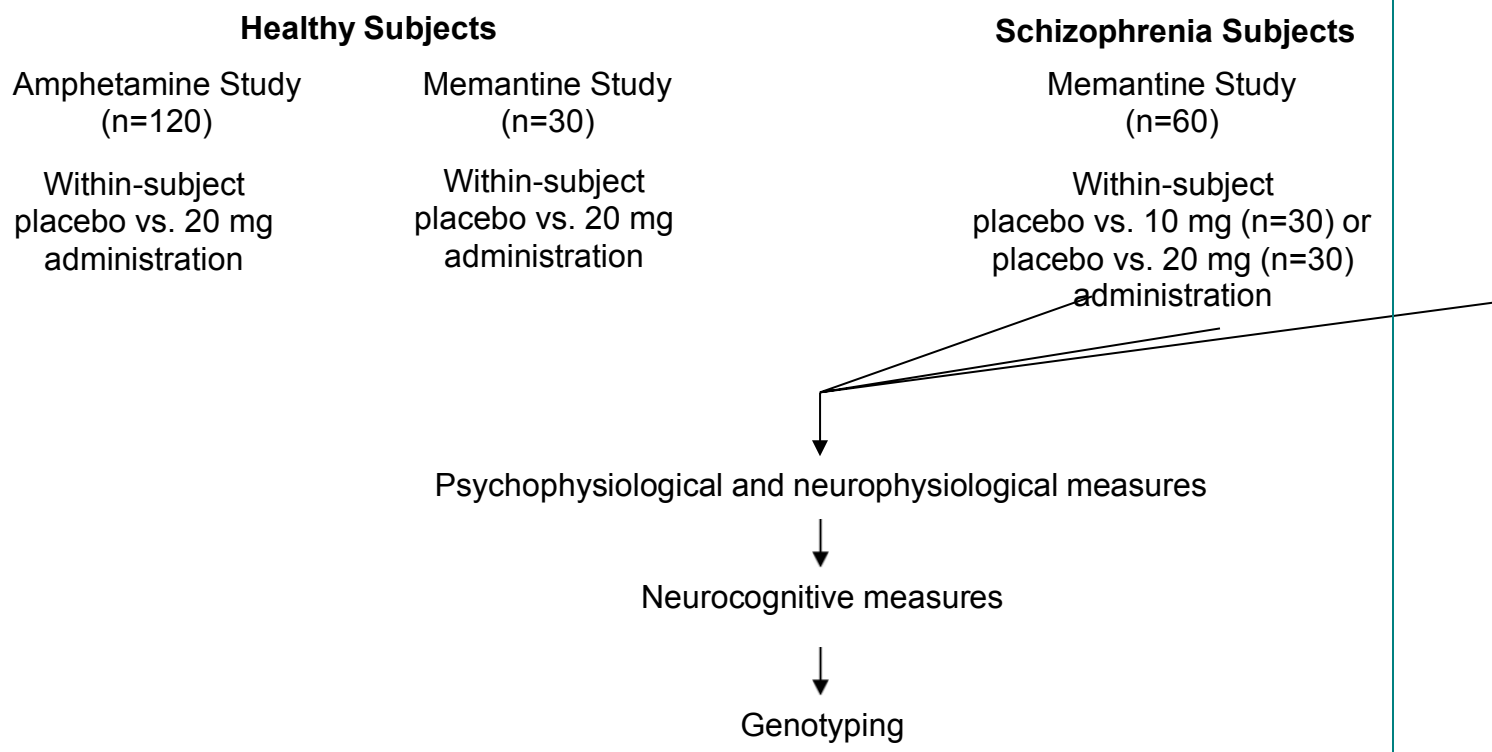
Our current studies are designed to achieve 3 Specific Aims (see Figure 1):

1. To assess the effects of the indirect dopamine agonist, d-amphetamine, on PPI and neurocognition in healthy subjects, and the moderating roles of personality and genotype in these effects. 120 healthy subjects will complete a within-subject study of placebo vs. 20 mg amphetamine (p.o.) on two separate days, completing measures of sensorimotor gating and neurocognition on each test day. All subjects will be characterized in terms of specific genetic and personality characteristics.

2. To assess the effects of the NMDA antagonist, memantine, on PPI and neurocognition in healthy subjects, and the moderating roles of personality and genotype in these effects. 30 healthy subjects will complete a within-subject study of placebo vs. 20 mg memantine (p.o.) on two separate days, completing measures of sensorimotor gating and neurocognition on each test day. All subjects will be characterized in terms of specific genetic and personality characteristics.

3. To assess the effects of the NMDA antagonist, memantine, on PPI and neurocognition in schizophrenia patients, and the moderating roles of genotype in these effects. 60 well-characterized and clinically stable individuals with schizophrenia will complete a within-subject study of placebo vs. 10 mg memantine (p.o.) (n=30) or placebo vs. 20 mg memantine (n=30) on two separate days, completing measures of sensorimotor gating and neurocognition on each test day. All subjects will be characterized in terms of specific genetic characteristics.

Figure 1. Schematic "flow chart" of current studies



7. BACKGROUND AND SIGNIFICANCE

The startle reflex is a constellation of responses to sudden, relatively intense stimuli that is usually classified as a defensive response. One major advantage of startle response paradigms is that the same phenomena can be studied across species. In humans, the blink reflex component of the startle response is measured using electromyography of the orbicularis oculi muscle. Despite its simplicity, startle demonstrates several forms of plasticity - including habituation and fear-potentiation - that are regulated by forebrain circuitry. Even these more complex processes exhibit striking similarities across species, from rodents to humans. One form of startle plasticity is "prepulse inhibition" (PPI), which is the normal suppression of the startle reflex, which occurs when the intense startling stimulus is preceded by a weak prestimulus.

In PPI, a weak prepulse inhibits a reflex response to a powerful sensory stimulus. PPI occurs when the prepulse and startling stimuli are in the same or different sensory modalities. PPI also occurs in virtually all mammals and primates, including humans. It is not a form of conditioning, since it occurs on the first exposure to the prepulse and pulse stimuli, and it does not exhibit habituation or extinction over multiple trials. PPI thus appears to reflect the activation of a ubiquitous "hard-wired" centrally mediated behavioral "gating" process. The PPI paradigm has been widely applied in studies of information processing in normal animals and humans. The inhibitory processes activated by the weak "prepulse" and the resulting decrement in startle amplitude are used in an operational definition of sensorimotor gating: the degree to which startle amplitude is inhibited by a prepulse is a measure of the amount of sensorimotor gating.

Our interest in PPI as a measure of sensorimotor gating grew from the observation that human disorders characterized by dysfunction in brain substrates that regulate PPI are accompanied by evidence of

impaired cognitive or sensorimotor inhibition. Thus, our laboratory and others have reported impaired PPI in patients with Schizophrenia, Obsessive Compulsive Disorder (OCD), Huntington's Disease, nocturnal enuresis and Attention Deficit Hyperactivity Disorder or Tourette's Syndrome. These disorders are all characterized by a loss of gating in sensory, motor or cognitive domains, and are characterized neurologically by abnormalities in cortico-striato-pallido-pontine circuitry that modulates PPI.

Over the past 20+ years, the PI and colleagues have systematically studied the neural substrates of PPI in rats. These studies have revealed that PPI is regulated by sequential neural connections between limbic cortex (temporal and medial prefrontal cortex), the ventral striatum, the ventral pallidum and the pontine tegmentum. This limbic cortico-striato-pallido-pontine circuitry then interfaces with the primary startle circuit at the level of the nucleus reticularis pontis caudalis. The neurotransmitters active at each level of this circuitry have been studied as well: the cortico-striatal interface involves interactions between glutamate and D2 dopamine receptors; the striato-pallidal input is GABAergic, as is the pallido-pontine input. Thus, by identifying patterns of PPI deficits in neuropsychiatric populations, we are able to use this information to understand the pathophysiology of these disorders, as well as to develop strategies for designing optimal drug treatments. We have already made significant steps towards these ends.

Some evidence already suggests that findings from preclinical studies of the neural substrates regulating PPI can "cross species" and be applied to humans. For example, PPI is disrupted in patients with Huntington's Disease (HD), and in rats with cytotoxic lesions of striatal regions that model features of the pathophysiology of HD. Preliminary studies suggest that the "cross-species" parallels of this measure can also be demonstrated with pharmacologic probes: PPI is disrupted in both rats and humans by indirect DA agonists (e.g. amphetamine) and by direct DA agonists (e.g. bromocriptine and apomorphine). These pharmacologic studies of PPI in humans are not fully compelling at this time, since they were either performed only in small samples, or in patients with neurologic disorders (e.g.. Parkinson's Disease) that might complicate interpretation of the findings as they relate to the normal neural regulation of PPI.

More recent studies have clarified that the sensitivity of PPI to drug effects in normal humans is moderated by several factors, including the presence of specific genes, and personality dimensions associated with those genes. For example, several groups have reported that PPI and its sensitivity to drug challenge differs significantly between normal men who carry different alleles for the COMT Val158Met polymorphism. In these studies, the Val/Val allele is associated with high COMT activity, rapid DA catabolism, high novelty seeking scores, low basal PPI and PPI-enhancing effects of the COMT inhibitor, tolcapone. In contrast, the Met/Met allele is associated with low COMT activity, low DA catabolism, low novelty seeking scores, high basal PPI, and PPI-reducing effects of tolcapone. We previously reported that rats expressing high levels of COMT within the ventral striatum exhibit PPI-enhancing effects in response to DA agonists, like amphetamine, while rats expressing low levels of COMT in this region exhibit PPI-reducing effects in response to amphetamine. More recently, we confirmed that normal women with high novelty seeking scores (who as a group predominantly express the Val/Val high activity COMT allele) respond to amphetamine with elevations of PPI, while those with low novelty seeking (associated with the Met/Met low activity COMT allele) respond to amphetamine with reduced PPI. We also detected PPI-enhancing effects of the NMDA antagonist and weak DA agonist, memantine, among men exhibiting low baseline PPI and/or high novelty seeking, both of which are associated with the Val/Val COMT genotype. Thus, across species, genetically determined levels of COMT activity appear to moderate the impact of specific drugs on sensorimotor gating. These findings suggest a biological explanation for a genetically based "vulnerability" to the gating-disrupted effects of increased dopamine activity and/or reduced NMDA activity, thought to be core features of brain disorders such as schizophrenia and Tourette Syndrome. We now plan to extend this work to further clarify the role of COMT polymorphisms and other genetic substrates on the sensitivity of PPI to drug effects in humans.

The most recent development in our studies has emerged as other groups, as well as our own, have reported that levels of PPI are significantly associated (correlated) with specific neurocognitive processes, including measures of executive functioning and working memory. In the process of our pharmacological

studies of PPI, we identified specific agents (e.g. memantine) that increased PPI, particularly among individuals with specific physiological (e.g. low baseline PPI) and psychological (e.g. high novelty seeking) "biomarkers" associated with the Val/Val COMT polymorphism. These two lines of findings led us to test whether such drug-induced increases in PPI predicted increases in neurocognitive functions in biomarker-identified subgroups. If so, we might be able to develop laboratory-based measures for predicting procognitive drug effects in patient populations - particularly among disorders associated with impaired PPI and working memory, such as schizophrenia.

In total, we expect to accomplish three goals by extending a new line of research, investigating the effects of specific pharmacologic agents on PPI and other psychophysiological measures in humans:

1) Extension of the preclinical findings into humans, to allow interpretation of anatomical and genetic correlates of observed behavioral deficits in psychiatric patients.

2) Replicate and extend findings in humans with specific pharmacologic probes.

3) Determine the relationship between specific drug effects on PPI and neurocognitive functions, in healthy and patient populations, as a function of specific physiological, psychological and genetic biomarkers.

8. PRELIMINARY STUDIES/PROGRESS REPORT

Psychophysiological measures and some other aspects of the protocol described in this application have been used for the past thirteen years in the PI's laboratory. No untoward effects have been observed. The success of the protocol in evaluating sensorimotor gating encouraged us to expand this protocol to include the use of pharmacologic agents. Results from our control population led to modifications in experimental designs that facilitate the detection of subtle drug effects and differences in control vs. patient populations.

Previous work of this type has been completed successfully at this institution and elsewhere. Specifically, Dr. David Braff undertook studies of the effects of d-amphetamine on PPI in humans, and the present PI was a co-investigator on that protocol (91-516), which has now expired. The PI pursued studies of the effects on PPI in humans of the NMDA antagonist ketamine, in collaboration with Dr. Mark Wallace (96-0003); ketamine and other NMDA antagonists disrupt PPI in rats. Studies at other institutions have examined the effects of caffeine, ketamine, apomorphine, amphetamine, nicotine or bromocriptine on PPI (the latter given alone, and in combination with haloperidol); as in rats, these studies report that PPI can be disrupted (apomorphine, amphetamine, bromocriptine, ketamine) or enhanced (nicotine) in humans, and that the PPI-disruptive effects of DA agonists can be prevented by the D2 antagonist haloperidol. In some cases, a lack of consistent drug effects on PPI in humans demonstrated parallel “negative” effects of pharmacological probes on PPI across species. While PPI measures had already been completed in humans using some of the drugs in this proposal, other proposed drugs had not been tested (e.g.. amantadine, pergolide, and quetiapine). The PI under this protocol has now completed studies with these drugs, in addition to caffeine, bromocriptine and amphetamine, and proposed studies will include memantine (see below). Thus, the proposed studies are designed to both replicate and extend the literature of the pharmacology of PPI in humans.

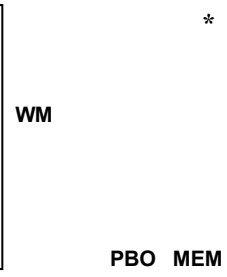
As described in our past progress reports, we continue to actively test subjects using our proposed measures. They include bilateral measures of eyeblink acoustic startle, prepulse inhibition and habituation of acoustic startle, visuospatial priming and latent inhibition. Additional variations of these measures are developed on a regular basis to enhance their sensitivity.

After completing a series of studies using the non-DA stimulant caffeine, we undertook a systematic series of studies to examine the effects of DA agonists on startle and related measures in normal humans. We assessed the time course of action of several DA agonists - pergolide (0.025 and 0.1 mg), amphetamine (20 mg), amantadine (200 mg) and bromocriptine (1.25 and 2.5 mg) - on startle measures,

autonomic changes, and self-ratings of somatic and physiological symptoms. We then completed detailed, within-subject studies of the effects of amphetamine, amantadine, bromocriptine and pramipexole on PPI and related measures. Findings from these studies were described in published reports, cited in Section 22, and many have already been replicated and extended by other groups.

Most recently, we have begun to assess the broader neurocognitive correlates of drug-induced changes in sensorimotor gating. Our group and others have reported that levels of PPI correlate significantly with global neurocognitive measures, and specifically, with working memory (WM); in schizophrenia patients, we reported that levels of PPI correlate significantly with global levels of functioning. We also reported that the Alzhemier's Disease medication and NMDA antagonist, memantine, significantly increases PPI, particularly among individuals with phenotypes - low baseline PPI and high novelty seeking - associated with the Val/Val COMT genotype. As a result, we have initiated studies in normal subjects to test the hypothesis that memantine will increase WM, particularly among subjects exhibiting high memantine PPI sensitivity. Our initial findings in a double-blind, within-subject, balanced order, placebo-controlled study, are quite promising: memantine (20 mg po) significantly increased WM in normal subjects, despite the fact that most of these subjects are UCSD undergraduate students with high baseline levels of WM (see figure, right). PPI was also significantly increased in these subjects, particularly among the predicted "sensitive" subgroups.

Effects of memantine (MEM) vs. placebo (PBO) on WM (%ile score from MCCB, see text). WM was increased by MEM in 7 out of 8 subjects, and unchanged in the 8th. In these subjects ($F=10.68$, $p<0.015$), MEM also significantly increased PPI. This ongoing study is conducted with a double-blind, balanced order design.



The implications of these preliminary findings are potentially quite significant, as they suggest that MEM might enhance PPI and WM, particularly among subgroups of individuals carrying "biomarkers" that include low baseline PPI, high novelty seeking, and/or the Val/Val COMT genotype. If this same pattern of results is detected in clinical populations, it will suggest a means to prospectively identify patients in whom memantine (or other putative pro-cognitive agents) can enhance specific neurocognitive abilities (e.g. WM) to synergize with therapeutic interventions (e.g. cognitive training) that rely on these abilities. We are currently planning to test this prediction in clinical populations, including patients with schizophrenia, who are enrolled in IRB-approved clinical trials of cognitive training.

Summary of Progress to Date

A. Drug Effects on Prepulse Inhibition of Startle:

1. We carefully examined the effects of 4 dopamine agonists (amphetamine, 20 mg), bromocriptine, 1.25 mg), pramipexole (0.125 and 0.175 mg) and amantadine, 200 mg) and one NMDA antagonist (memantine, 20 and 30 mg) on prepulse inhibition (PPI) and related measures, and reported on these effects in five papers (below). Paradigms were modified to increase the sensitivity to drug effects (e.g. via use of within-subject designs or optimal stimulus parameters), and new paradigms were developed to provide new insights into these drug effects (e.g. via the development of a novel sensory gating paradigm). Our findings identified quite distinct effects of these drugs in our behavioral paradigms; for example, amphetamine on the one hand, and amantadine and memantine on the other, produced opposite effects on PPI, with amphetamine significantly disrupting and amantadine and memantine significantly increasing PPI. These effects were not predicted based on our preclinical findings in rats, and have led to new hypotheses and insights related to cross-species differences in the regulation of sensorimotor gating.

2. We studied the effects of an atypical antipsychotic (Seroquel) on PPI and related measures in normal male subjects, the first of its kind in the literature. Seroquel (12.5 mg) was used without any adverse effects on normal males. This initial study helped us design our current, ongoing experiments, examining

interactions between Seroquel and amphetamine and between Seroquel and amantadine, using the dose of the DA agonist as a within-subject variable and Seroquel dose as a between-subject variable. Furthermore, our experience with Seroquel led to a contract for a specific study with AstraZeneca Pharmaceuticals, which has been completed. The contract with AstraZeneca expired at study completion. During this research period, all of our human drug studies have been relocated to the GCRC at the UCSD Medical Center with the option to test at the UCSD Clinical Teaching Facilities.

3. We have recently detected pro-cognitive (WM) effects of memantine (20 mg) among normal controls who also exhibit PPI-enhancing effects of this drug (see above).

B. Paradigm development

Studies led to the development and optimization of two paradigms: a) a within-subject latent inhibition (LI) paradigm that was studied both in normal controls treated with DA agonists, and in normal control vs. schizophrenia subjects. Developing a within-subject LI paradigm suitable for human use has been a longstanding goal of our psychophysiology program.

C. Relationship of physiological and personality measures to startle gating in normal subjects

As part of our ongoing process of screening normal control subjects for drug studies, we have collected data from large samples (current n > 400), adequate for examining relationships between sensorimotor gating and normal physiological and personality markers, as well as factors such as ethnicity, that may ultimately be relevant to genetic studies with PPI. These studies have led to several interesting findings, including an inverse relationship between resting blink rate (a physiological variable related to central DA function) and PPI, as well as robust ethnic differences in startle magnitude (but not sensorimotor gating) between Caucasian and Asian American populations.

We have had no adverse reactions associated with drug ingestion in any of our testing, including tests completed with DA agonists, Seroquel, or drug combinations. Nausea previously experienced by a small number of test subjects after pergolide was reported in a previous IRB update; we have not since used pergolide in any studies. One brief syncopal episode during venopunture was recently reported, but had no long-term sequellae. The DA agonists used for the majority of the studies during this period were amphetamine and amantadine, which are very well tolerated. Seroquel results in mild sedation, but subjects remain quite comfortable. All other drugs, experimental measures, testing procedures, etc. proposed for studies in this application have already received UCSD IRB approval in Project #031317.

Several modifications to the protocol have been approved and incorporated into the protocol.

*REFERENCES ARE LISTED IN SECTION 22

9. RESEARCH DESIGN AND METHODS

GENERAL METHODS:

a) Study populations: Study subjects, ages 18-45, are recruited from the community. Two subject populations are recruited: clinically normal control subjects, and patients with schizophrenia. The patient populations and upper age limit of 45 are used only for studies with memantine, which is prescribed clinically in geriatric populations for the treatment of Alzheimer's Disease. For all other studies, the sample is limited to clinically normal controls and the upper age limit is 35.

b) We ask new participants whether they would allow us to contact them regarding future studies. If they agree, our plan is to contact them at a future date for appropriate IRB approved studies.

c) For all drug evaluation studies, normal control subjects are recruited and screened for evidence of physical or psychological impairment; schizophrenia patients are recruited and screened only for

participation in drug evaluation studies with memantine. Each recruited subject is given a complete physical and psychiatric examination including medical, psychiatric, social and drug histories, an EKG and a urine test. For most studies, only male subjects, ages 18-35, are recruited. For a subset of studies, female subjects, and subjects up to age 45 will be recruited, as discussed below. All subjects are asked to arrange for transportation to and from any test session due to possible adverse effects for up to 12 hours after drug administration. During some or all of the tests the subject's performance may be monitored by the use of a non-recording camera. This is to ensure that the subject is awake and performing the task as instructed. Only the investigator running the test session will be able to see the subject, and this allows quantification of blink rate.

d) Subject payment (also see below, section 18): For subjects participating in the "Within-Subject" test sessions, payment will be divided in the following schedule: on completion of screening day: $30; on completion of first TEST SESSION day: $100; On completion of second TEST SESSION day: $130. This payment schedule provides appropriate incentive for the subjects to return for the second test day. This is to ensure that subjects return for the second and third test days. If subjects fail screening criteria for recreational drug use prior to any TEST SESSION day, they will not be tested further and will not be paid for that test day. We will recommend that subjects remain in our laboratory for monitoring until six and one half hours after pill ingestion. Should they choose to leave our facility for any reason prior to that time, it will be at their own risk. Their involvement in the study will be completed and payment on the Test Session day will be prorated to $16 per hour.

e) Venopuncture: Venopuncture for COMT allelic testing in some subjects will occur during the initial visit, before or after what normally is titled the SCREENING SESSION in the studies listed below. A single venopuncture performed by certified individuals within the UCSD Medical Center GCRC/CTRI or Blood Drawing Station will be used to 10 cc of blood for COMT allelic testing. Based on specific needs of the experimental design (e.g. equal number of Met/Met, Val/Met and Val/Val allelic carriers, or subgroups of "high" vs. "low" PPI levels, based on the upper vs. lower quartile of a normal population distribution), subjects may be asked to come back for further testing, if they indicate they would like to do so. If participants continue to the remainder of the study, there will be 2 test days, one of which will involve placebo, and the other day involving an active dose of amphetamine (20 mg), memantine (20 mg) or other approved test drug/dose. The TEST SESSIONS will mimic those in the WITHIN-SUBJECT model below; however, venopuncture occurs only during the first visit.

f) Clinical assessment: Specific clinical assessment tools used in control and schizophrenia subjects are described in Section 10.

g) Test schedules:

1. The "WITHIN-SUBJECT" study involves a single drug. There will be 2 test days – on the additional test day, subjects will receive either placebo or an active dose of one of the following: amphetamine (20 mg), memantine (10 mg) and memantine (20 mg). Some studies may require a venopuncture for genetic analysis as discussed above. A "model" example of a WITHIN-SUBJECT test schedule is shown below:

Test Day 1

0815-0845 Subject signs required forms, provides urine sample, eats standardized breakfast, venopuncture (if required)
0845-0900 Vital signs (VS) check, hearing and vision test, symptom rating scale.

0900-0915 drug or placebo administration.
0915-0930 VS check; symptom rating scales.
0930-0945 EMG electrodes applied.
0945-1000 VS check; symptom rating scales.

1000-1125 Startle response measurement, including PPI, habituation and intensity assessment.
1125-1140 VS check; symptom rating scales.
1140-1155 Visual LI or Visuospatial priming or MCCB
1155-1210 VS check; symptom rating scales.
1210-1300 Subject offered lunch from cafeteria.
1300-1600 VS check hourly; subject dismissed if VS within established parameters at 1600.

Test Day 2: 7-30 days after Test Day 1

0815-0845 Subject signs required forms, provides urine sample, eats standardized breakfast, venopuncture (if required)
0845-0900 Vital signs (VS) check, hearing and vision test, symptom rating scale.

0900-0915 drug mg or placebo administration: WHICHEVER DOSE WAS NOT RECEIVED ON TEST DAY 1
0915-0930 VS check; symptom rating scales.
0930-0945 EMG electrodes applied.
0945-1000 VS check; symptom rating scales.
1000-1125 Startle response measurement, including PPI, habituation and intensity assessment.
1125-1140 VS check; symptom rating scales.
1140-1155 Visual LI or Visuospatial priming or MCCB
1155-1210 VS check; symptom rating scales.
1210-1300 Subject offered lunch from cafeteria.
1300-1600 VS check hourly; subject dismissed if VS within established parameters at 1600.

Subjects will be instructed to not eat on the morning of the test, and instead will be served a standardized meal 30 min prior to drug administration, so as to maintain a controlled and consistent impact on drug absorption.

Vital sign assessment during and after testing will be performed in lying, sitting and standing positions, by a trained researcher or health professional. Sessions will be discontinued for 55>HR>110, 90> SBP>160, 45>DBP>95, emesis, severe discomfort or other unanticipated medical or psychological consequence. At the end of testing, at the times described above, subjects will be dismissed if their heart rate is between 55 - 90, their SBP is between 90 -150, their DBP is between 45 - 90, and there is no evidence of dizziness or significant heart rate increase or blood pressure reduction on postural changes, from lying to sitting to standing.

2. The "ONE-DAY" test session: When developing new test sessions, we often examine correlations between response characteristics elicited by different stimulus parameters. The subjects participating these types of studies will be tested with air puff and all acoustic stimuli. Acoustic stimuli will be no louder than 118 dB(A), a level already approved in previous protocols (most recently 071154). No drugs are administered during these studies.

These studies will include up to 50 normal control subjects per year. Some subjects may be screened on the phone and in person, as done in previous studies. The consent form used will have the different possible tests listed. The options are:

1. A urine test will be required to test for the presence of illicit drug use. Your study participation will be terminated if the urine test is positive for any drugs, and you will be paid for your time, which will be prorated as stated below. Only the researcher will know the results of the test. This procedure takes approximately 10 minutes.
2. You will be asked to fill out several personality questionnaires. You can skip any questions you do not want to answer. This procedure takes approximately 30 minutes.
3. You will be a given a psychiatric examination that includes medical, psychiatric, social and drug histories. This procedure takes approximately 20 minutes.

4. Eyeblink startle: two electrodes with adhesive backing will be placed next to both eyes so that your blink reflex can be measured, and one will be placed behind the left ear as a reference measure. This procedure takes approximately 10 minutes. The procedures listed below may occur concurrently.
5. You will be asked to complete one or more computer task(s), each approximately 15 to 20 minutes.
6. You will be asked to listen to a series of brief tones, experience a series of air puffs under your chin, and/or experience a series of brief vibrations delivered via speaker to your hand for approximately 25 minutes. Some of the tones will be so loud that you might find them annoying or uncomfortable. Some puffs and vibrations might be so strong that you might be surprised.
7. You will be asked to make marks on a piece of paper in response to the tones.
8. You will be asked to evaluate your present mood state in a questionnaire.
9. You will be asked to make a mark on a line to indicate how loud a sound seems to you with a pencil, or by using a computerized rating scale called the "slider" that has a knob on its surface. Movement of the knob corresponds to movement on a computer screen, which will sit in front of you.

The participant will be informed over the phone that some or all or the options may not be used, and will not be a part of the procedure.

h. Information pertaining to specific pharmacologic agents to be used in these studies:

Proposed list of pharmacologic agents and doses (doses based on previous human studies with these agents, or the lowest dose initiated in standard treatment algorithms, as described by the Physician's Desk Reference):

Drug	Route	Doses	"Common" side effects (single dose)*
Amphetamine	Oral	20 mg	Increased HR, BP, restlessness, dizziness, euphoria
Memantine	Oral	10, 20 mg	Dizziness, restlessness, nausea, headache

- most reports define "common" to either mean >5% incidence or >10% incidence; most side effects reported only with continued use or repeated dosing, rather than single dose use, and typically occur with doses substantially higher than those to be used in this study, or in vulnerable clinical populations (e.g. elderly patients with dementia); in several cases, these effects were observed at rates that were not statistically different from placebo.

The dose of amphetamine used in this study (20 mg po) is one that is used commonly in healthy adult subjects. References are provided below for examples of studies in which this dose has been used, without untoward effects; two papers from our studies are included among these. Subjects in our studies are 18 - 35 years old, and are carefully screened by a physician, or a nurse under supervision of a physician, who takes a medical history and performs a physical examination. Screening also includes an EKG and urine toxicology tests.

Medications are administered in the UCSD Clinical Teaching Facility, rooms A-304A and A305, which are staffed by a physician or registered nurse. To date, amphetamine as a single 20 mg oral dose has been administered to 65 subjects in our studies, 49 in a within-subject double-blind placebo-controlled study, and 16 in a between-subject double blind study. No subjects reported adverse effects of this dose of amphetamine. Measures of autonomic function indicated the expected increases in heart rate and blood pressure after amphetamine, as indicated below. However, in each case, these increases were numerically small (see Table 1) and did not approach levels that would normally be of medical consequence in a healthy young adult population. Only one subject exhibited a heart rate with amphetamine in excess of 100; several placebo subjects exhibited heart rates in the 90's.

Table 1. Autonomic effects of 20 mg d-amphetamine po in 65 subjects tested to date

	Placebo	Amphetamine
Ave. Heart Rate during test session (mean (SEM))	66.55 (1.24)	68.92 (1.14)

Maximum HR (mean (SEM))	73.27 (1.40)	75.94 (1.49)
SBP (mean (SEM))	113.15 (1.74)	116.65 (1.54)
DBP (mean (SEM))	67.23 (1.01)	70.02 (0.86)

Subjective ratings also demonstrated no adverse effects of this drug dose, based on visual analog scale (VAS) self-assessments (Table 2). In these scales, 0 = no effect, 100 = extreme effect. Other scales indicated that this dose of d-amphetamine reduced drowsiness, and was associated with a trend towards an increased sense of being "happy".

Table 2. VAS scores for subjective effects of 20 mg d-amphetamine po in 65 subjects tested to date

	Placebo	Amphetamine
Dizzy (mean (SEM)	2.73 (0.68)	3.04 (0.76)
Queasy (mean (SEM))	2.10 (0.52)	1.78 (0.30)

Summary: A 20 mg po dose of amphetamine is used commonly in the published literature in studies of normal, healthy adults, without common adverse reactions. This experience is validated in our own studies of 65 normal adult subjects.

References are included at the end of this section.

Memantine is the only drug in this application that is being proposed for testing in schizophrenia patients. It is FDA-approved for the treatment of dementia, but has been widely used in a number of different clinical conditions (see below).

Memantine, Basic Information: The NMDA receptor is a ligand-gated ion channel, permeable to monovalent and divalent ions. Activation of NMDA receptors leads to Ca++ influx, which is blocked by NMDA channel blockers. High affinity channel blockers, like PCP, are not easily studied in man, due to side effects such as psychosis and neurotoxicity. However, low affinity channel blockers are used clinically, and are well tolerated, with potential neuroprotective properties. Several lower affinity NMDA antagonists reduce long-interval PPI, though this effect is generally weaker than that caused by high affinity antagonists. Wiley et al. reported PPI-disruptive effects of dextromethorphan and memantine; the effects of memantine were dose-related, reaching significance at 10 mg/kg (an effect that we have replicated), while those of dextromethorphan were evident only at the highest dose (100 mg/kg). At these doses, neither drug altered startle magnitude, while a lower affinity NMDA antagonist, ibogaine, reduced PPI only at doses that significantly depressed startle. In this report, amantadine did not alter PPI at a dose (56 mg/kg) lower than the one we have found to reduce long interval PPI, and to increase short interval PPI (100 mg/kg).

Memantine, Clinical Information: Memantine has been prescribed in Europe for > 15 years for dementia, with formal EU marketing approval. Published studies document safety and high tolerability in >1000 elderly patients with dementia, and tolerability of doses 2-4X above typical therapeutic ranges in normal, younger adults, who reported no adverse effects at a dose of 40 mg po. The active dose in the present proposal (20 mg po) is one-half the dose found to be well-tolerated in studies in these younger male subjects. Studies have reported no neuropsychological changes or mood changes after administration of 20-40 mg memantine po in healthy young men, and only a short-lasting sensation of restlessness and dizziness in 4 out of 7 healthy young adults, 2 hours after administration of 30 mg memantine po. Other studies using intravenous loading of memantine in healthy young adults reported no side effects.

Memantine was developed for many clinical indications (e.g. dementia, neuropathic pain and diabetic neuropathy). Full FDA approval was received 10/17/03. Since its approval, memantine has been prescribed widely, both for its FDA indication of mild-to-moderate dementia, and off-label, for more severe dementia, and for other conditions, including diabetic neuropathy. Data continue to support its excellent safety profile; a recent study reported in JAMA with > 200 subjects treated daily with 20 mg memantine

resulted in fewer treatment discontinuations due to adverse events for memantine (7.4%) than for placebo (12.4%). Memantine is prescribed routinely for patients at the UCSD Medical Center Senior Behavioral Health Unit; these patients are studied in the PI's protocol before and after initiation of memantine therapy. Thus, in essence, the current request for an amended protocol will extend our existing studies in elderly, medically complex patients to include healthy, younger, normal control subjects.

Based on our published and unpublished findings to date, we have studied memantine in a full placebo-controlled double-blind cross-over design in 45 clinically normal individuals. Data from 37 subjects was reported in a published paper (20 mg, n = 19; 30 mg, n = 18), and data from 8 addition subjects (20 mg) was recently submitted as an abstract for the upcoming 2010 meeting of the Society for Neuroscience. No AEs were detected with any subjects in these studies.

The present protocol proposes the use of 10 and 20 mg memantine; our experience to date is limited to the higher of these two doses (20 mg); based on the published literature, we expect any potential AEs to be dose-dependent, and thus the 20 mg dose (vs. the 10 mg dose) represents the one with the highest likelihood of AEs, should any occur. In our published data (n=19), the only detectable impact of 20 mg memantine (other than those in our neurophysiological measures) were: 1) an increase in self-reported level of happiness 30–230 min after pill administration; and 2) a small decrease in spontaneous blink rate, an effect generally suggestive of reduced fatigue or somnolence. No significant changes in self-rated dizziness, queasiness or drowsiness were detected at any time after 20 mg memantine. Autonomic measures (heart rate, systolic or diastolic blood pressure) were also not significantly changed by memantine. Our unpublished data (n=8) with 20 mg memantine (see above), confirms all of these findings, including no significant change in autonomic measures or self-rated dizziness, queasiness or drowsiness, a trend towards increased self-rated happiness and decreased blink rate. In addition, as described above, we noted a significant increase in working memory after memantine, as measured by the MCCB.

Memantine has been studied in schizophrenia patients. It is important to note that these studies involved daily dosing for many weeks or longer, while the present protocol proposes only a single active dose of memantine. Nonetheless, the findings are informative:

Memantine use in schizophrenia patients: A recent double-blind study reported large reductions in positive and negative symptoms (d=1.38-3.33) and improved Mini-Mental State Exam scores after 12 weeks of memantine (20 mg/d; n=10) vs. placebo (PBO; n=11) added to clozapine; so significant adverse events were reported. An earlier 8-week double-blind, study of memantine (20 mg/d; n=70) vs. PBO (n=68) added to atypical APs detected no change in positive or negative symptoms or Brief Assessment of Cognition in Schizophrenia scores, but found that memantine was associated with more adverse events (AEs; memantine vs. PBO = 8.7% vs. 6.0%) and treatment discontinuation due to AEs (11.6% vs. 3.0%). Importantly, the most frequent serious AE in memantine group patients was an exacerbation of schizophrenia symptoms, but this AE actually occurred LESS OFTEN in the memantine group (2.9%) than in the placebo group (6.0%). Overall, the incidence of ANY adverse events over the 8 week trial was 92.4% in the placebo group vs. 88.3% in the memantine group; no changes in autonomic measures, EKG, laboratory measures or extrapyramidal functions were detected with memantine. A smaller, 6-week, open label study of memantine (5 - 20 mg/d) in symptomatic schizophrenia inpatients reported a significant improvement in positive and negative symptoms but not cognitive performance, with no AEs. Three case reports described beneficial effects of memantine (5 - 10 mg/d) in schizophrenia patients, with reductions in negative symptoms and functional impairment and no AEs; in two reports, symptoms returned on memantine discontinuation and resolved again after restarting memantine.

All drugs/doses proposed in this application (for amphetamine and memantine) are equal to or lower than those already approved by this IRB and studied in the PI's laboratory for several years in > 170 total normal adult subjects, with no adverse reactions. These doses are at or near the lowest recommended starting dose of a given medication when it is used in a clinical setting, and well below the typical

maintenance dose of these medications.

Drugs will be dispensed by a licensed physician, and a licensed physician will be present on the premises at all times during testing.

No drugs will be used in studies with subjects < 18 years of age. Nonetheless, it is reasonable to ask whether these drugs have been used safely in 18-35 year old subjects (or, in the case of memantine, 18-45 year old subjects). Although dopamine agonists have primarily been used and tested in Parkinsonian patients, some of these dopamine agonists are used in children. Amphetamine is used safely and effectively in children with Attention Deficit Disorder. The only drug in this proposal that does not have a specific indications or common use in adolescents is memantine. We have published findings of memantine's safe use in 18-35 year old study subjects, as described above. The fact that memantine is most often used in patients with multi-system medical illness (Alzheimer's Disease) accounts for some of its rare but more significant side effects (e.g. hallucinosis).

i. Laboratory Measures:

1. Startle Reflex: The startle reflex will be measured in control populations in men and women to examine sex differences in the startle-facilitating and inhibiting effects of weak and strong prepulses presented at short and long prepulse intervals. Sex differences in prepulse modulation of startle also will be measured using cross-modal stimuli (acoustic prepulse and tactile pulse). Sensorimotor inhibition and facilitation will be measured in women during different phases of the menstrual cycle.

Testing occurs during the light circadian phase (0900-1700). The testing room is maintained at 68-70° F. Subjects are screened for hearing impairment with a Saico Audiometer at .5, 1 and 6K Hz; impairment at 40 dB(A) leads to exclusion. Startle is measured with an SR-LAB IBM PC computer monitoring system and a custom EMG amplifier with a 1K Hz band pass filter. Subjects sit in a quiet room, with 2 Beckman miniature Ag-AgCl electrodes placed 1 cm lateral and inferior to the right and/or left external canthus, over the orbicularis oculi (R< 5K Ohm). A ground electrode is placed behind the left ear, over the mastoid. Subjects wear Telephonics headphones (TDH-39-P) and look forward to a point that allows them to be comfortable with their eyes open. A 5-min 70 dB (A) background white noise is followed by acoustic or air puff startle trials. The startle pulse is either a 118 dB(A) 40 msec noise burst (P-ALONE) or a comparably startling air puff stimulus presented alone or during prepulse trials, preceded at a 100 msec interval by a prepulse (20 msec noise burst a few dBs above background). Background white noise is continuous until the session ends. The session lasts about 25 minutes with repeated trials and an intertrial interval of 30 seconds.

Digitized blink responses are displayed graphically on the PC monitor; voluntary and spontaneous blinks are excluded based on published criteria. Startle reactivity is defined by P-ALONE amplitude. A small number of subjects are startle "non-responders": following criteria previously established, subjects whose startle amplitude does not exceed set levels are excluded from analysis of PPI (non-responder mean amplitude <10 units on P-ALONE, compared to typical "responder" mean of 75 units).

Tactile stimuli: In some studies, the subject rests their hand on a sound speaker that delivers a vibration to the thenar eminence of the dominant hand, followed 60-240 ms later either by 40 psi 40 ms air puff presented to the sternal notch or an acoustic 118 dB(A) or 105 dB(A) 40 msec noise burst.

2. Electroencephalographic (EEG) recordings and processing: EEG measures will be acquired using methods identical to those approved by this UCSD IRB for an existing protocol (#071128, PI: Dr. Greg Light), using a Neuroscan NuAmps system (Neuroscan Labs, El Paso, Tx). The EEG will be recorded from the scalp through 34 sintered Ag/AgCl electrodes using an electrode cap (EasyCap, Falk Minow Services). Electrodes placed at the tip of the nose and at Fpz will serve as the reference and ground, respectively. Four additional electrodes placed above and below the left eye and at the outer canthi of

both eyes will be used for monitoring blinks and eye movements. All impedances are kept below 4 kΩ. Signals will be digitized at a rate of 1 kHz with system acquisition filter settings at 0.5-100 Hz. Auditory stimuli will be presented to subjects using foam insert earphones (Model 3A, Aearo Auditory Systems). EEG and stimulus markers will be recorded continuously. Subjects will not smoke for at least 60 minutes prior to EEG recording and will be instructed to minimize eye movements and muscle artifact during the recording. During testing, subjects will be observed through a one-way mirror. In addition, signal quality and the number of sweeps free of gross artifacts (defined as ±100 μV across the 0 to 512 msec following stimuli) will be closely monitored. Data processing will be performed offline and blind to group membership using automated procedures. First, continuous recordings will be mathematically corrected for eye movement artifacts using established methods. Continuous data will be epoched relative to the onset of stimuli and centered at the mean of the prestimulus baseline. Following blink correction, epochs containing > ±50 μV will be automatically rejected. Epochs will also be manually reviewed to reject EEG segments with other artifacts (e.g., muscle activity). EEG testing, including electrode setup and running the two paradigms (MMN and gamma band entrainment) takes approximately 60 minutes.

Mismatch Negativity (MMN): Stimulation, recording, and analysis techniques for calculating MMN amplitude will follow our previously established methods. Briefly, Subjects will be presented with binaural stimulation (1 kHz computer-generated square wave stimuli, 85 dB[A] SPL, 1 msec rise/fall) with a fixed stimulus onset-to-onset asynchrony of 500 milliseconds. Standard (P=0.90; 50 msec duration) and deviant (P=0.10; 100 msec duration) stimuli will be presented to subjects in pseudorandom order while they watch a silent video. Signals will be digitized at a rate of 1 kHz with system acquisition filter settings at 0.5-100 Hz. MMN waveforms will be generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to the deviant tones. The MMN amplitude will be measured as the mean voltage from 135 to 205 milliseconds. Primary dependent measure: MMN amplitude at electrode Fz.

Gamma Band Entrainment (neural network synchronization to sensory stimuli): Evoked EEG power and inter-trial coherence analyses will be assessed in response to 20, 30, and 40-Hz stimulation at Fz following our published methods, as this is the electrode with maximal responses. The stimuli will be 1-millisecond duration, 93 dB clicks presented in 500 msec trains varying in rate of presentation (20, 30, and 40 Hz) in each of 3 blocks (order fixed). Blocks contain 200 trains of clicks with 500-millisecond intertrain intervals. For evoked power analyses, averages will be computed on 120 artifact-free epochs in each block and digitally filtered using a zero-phase shift, 10-60 Hz bandpass filter (24 dB/octave). The averaged epochs across the click trains (0-512 msec) will then be transformed into power spectra by means of fast Fourier transform (FFT) using a bin width of 1.95 Hz for the assessment of evoked power analyses. The 20, 30, and 40-Hz power spectra will be averaged across 10 Hz bands from 15-25 Hz, 26-35 Hz, and 36-45 Hz, respectively. Time/frequency ITC analyses will be performed using EEGLab in order to assess ITC of the stimulus-driven EEG signals. ITC provides an estimation of the strength of phase locking of the EEG signals across individual trials independent of the signal amplitude. In this analysis, a parameter is obtained that ranges from 0 (for non-phase locked, random activity) to 1 (for activity that is fully locked in phase across individual trials at a given latency). Considered together, the evoked power and ITC provide a conceptual framework for observing the event-related brain dynamics that occur consistently across both blocks of time and individual trials. Primary dependent measure: 40 Hz evoked power at electrode Fz.

3. Neurocognitive testing will consist of the MATRICS Consensus Cognitive Battery (MCCB), which includes ten tests that assess seven cognitive domains. The MATRICS battery was developed by an NIH Task Force for the purpose of testing drug effects on cognitive measures of relevance to schizophrenia. We are already using the MCCB for this purpose as approved in this protocol for control subjects, and will now also administer it to psychiatric patients. We previously used the MCCB for this purpose in another UCSD IRB-approved protocol (#071824). The battery takes about 1 hour to complete.

4. Visuospatial priming: The subject's task is to press one of four computer keys, which correspond spatially to four loci on a PC screen. Each trial includes two successive displays, each consisting of a brief

presentation of an 'X' and an 'O' in two of the four locations. On each presentation, subjects press the key corresponding to the location of the target letter 'O' while ignoring the distractor letter 'X'. The 'X' and 'O' within each display are visible for 150 msec; the time between displays is 350 msec. The task consists of 50 display pairs. There is a baseline condition in which the positions of the target ('O') and non-target ('X') in the probe display are unrelated to their positions in the prime display. In "repetition priming" (the facilitation condition) the position of the target remains the same on the successive displays. In "negative priming" (the inhibition condition) the target in the probe display appears in the location where the non-target had previously been.

5. Latent Inhibition: A computerized visual latent inhibition task is used. Subjects are pre-exposed or non-preexposed to a visual stimulus (pattern on a computer screen) that will, in the subsequent phase of the testing, have predictive value. Using the computer keyboard for responding the subjects will predict computer screen changes, being influenced by the earlier exposure parameter. Each phase requires 5 minutes time to run. Preexposed control subjects require more trials prior to reaching a criterion score on their predictive response.

Pregnancy test: The pregnancy test is able to detect tiny amounts of the pregnancy hormone hCG (Human Chorionic Gonadotropin) in urine. This hormone is produced in increasing amounts during the first part of pregnancy. HCG will be measured by a urine “dip-stick” (“Surecheck Early Pregnancy Test”). This test is a midstream format test for the detection of the pregnancy hormone in urine.

j. Statistics: Tests for homogeneity of variance are performed, and if appropriate, analyses of variance (ANOVA) used. Statview/Superanova software is used on the Macintosh. For startle data, P-Alone amplitude, PPI and startle latency are analyzed by ANOVAs; for drug studies, drug dose is used as a within-subject factor. Habituation is detected by a significant effect of trial block. Visuospatial priming is analyzed separately for baseline, facilitation, and inhibition conditions using ANOVAs. Baseline is a measure of visuospatial response time, while facilitation and inhibition scores are measures of sensorimotor modulation. Nonparametric statistics are used for the Latent Inhibition analyses because data from this test tend toward a bimodal distribution. A rank sum factorial analysis is used for the data. Other dependent measures will be analyzed with parametric or non-parametric analyses, generally consisting of mixed design ANOVAs, as appropriate. Following a significant ANOVA, specific comparisons are made using Tukey's tests. Alpha is 0.05.

Power considerations: Sample sizes vary across the different studies, based on issues ranging from the study design and goals to empirical evidence for effect sizes with the proposed drug or measure. For example, "ONE-DAY" studies are designed to identify and "pilot" optimal stimulus parameters for testing specific hypotheses, and these studies may not be powered to achieve traditional levels of statistical significance. On the other hand, designing studies of drug effects on PPI and related measures in control or patient populations requires detailed power information.

For example, to assess the effects of memantine on "gating" measures in schizophrenia patients, the primary measure will be evaluated by 2-way repeated-measure ANOVA of PPI with memantine dose and prepulse interval as within-subject factors. The hypothesis that memantine will increase PPI in schizophrenia patients will be confirmed by a significant effect of dose (active > PBO) or significant dose x interval (int) interaction and post-hoc comparisons at one or more prepulse intervals. Existing data (see above) provide a strong *a priori* prediction that the 120 ms prepulse interval will be most sensitive to PPI-enhancing effects of MEM. The effect size (d) for PPI-enhancement by 20 mg memantine in HCS was 0.91; with a similar “d” in patients, 30 patients/dose yields power of 0.92 to detect the predicted memantine effects; with maximum expected attrition (n=24), power is 0.85. Past findings also lead to the prediction that these MEM effects would be most robust in subjects exhibiting the lowest basal PPI levels (d=1.80). Using a median split of mean basal (screening) PPI levels, ANOVA as above will detect a significant interaction of memantine dose x basal PPI level, or dose x basal level x int, and significant post-hoc comparisons at one or more prepulse intervals (again, 120 ms being the strongest *a priori* candidate). Given the published “d” in control subjects, a comparable “d” in the proposed 12-15 “low PPI” patients/dose group would yield power >0.95 to detect the predicted memantine effects.

Lastly, based on the impact of basal PPI level and personality measures in controls, we hypothesize that a critical moderating factor underlying PPI memantine sensitivity is COMT Val158Met genotype; specifically, we predict that "Val/Val" individuals will be most sensitive to memantine-enhanced PPI. This will be tested in two ways: first, by ANOVA as above, with COMT status as a between-subject factor, and memantine dose and prepulse interval as within-subject factors. Significant genotype x dose or genotype x dose x int interactions, with appropriate post-hoc comparisons, would confirm the hypothesis. Estimating d=1.53, based on the mean "d" of two "COMT phenotypes" in controls – low basal PPI (d=1.80) and high "novelty seeking" personality (d=1.27) - the proposed 11 Val/Val and 7 Met/Met patients/dose group would yield power of 0.90 to detect genotype-sensitive memantine effects. It is possible that various factors (including a skewed distribution of allele frequencies, or substantial genotype effects on basal PPI levels) might preclude detection of a significant 2- or 3-way interaction. A secondary (albeit weaker) test of the hypothesis will utilize separate ANOVAs in Val/Val vs. Met/Met subgroups, with predicted PPI-enhancing effects of memantine in the Val/Val but not Met/Met subgroups. Previous reports also predict a significant main effect of genotype, with PPI levels following the Met/Met>Val/Met>Val/Val gradient. Logistic regressions might be used, with genotype coded to reflect "dose" of the Met allele (Val/Val=0, Val/Met=1, and Met/Met=2), to assess the distribution of the neurophysiological and neurocognitive measures. All analyses will be conducted independently for each dose group. If comparable effects are evident with 10 and 20 mg doses, dose groups may be pooled to increase power for exploratory analyses (e.g. to detect genotype x drug effects).

Main effects of memantine on WM will be tested by one-way ANOVA with memantine dose as a within-factor. Based on d=0.73 for increased WM after 20 mg MEM in controls (see above), the proposed 30 patients/dose group would yield power of 0.79 to detect significant WM-enhancing effects. While preliminary data yield less robust predictions for COMT subgroup sensitivities in memantine effects on WM performance, given the significant correlation of WM and PPI, and known impact of COMT genotype on PPI levels, we predict some differential (Val/Val > Met/Met) memantine sensitivity in this measure. If we estimate effects of COMT status on WM memantine-sensitivity to be comparable to those for PPI (65% increase in effect size), then the estimated d for Val/Val vs. Met/Met sensitivity should be 1.20, and the proposed genotype subgroup sizes would yield power of 0.65 to detect genotype-sensitive memantine effects on WM.

Secondary "biomarkers" are MMN and GBS. For MMN, positive memantine effects will be detected by increased MMN amplitude at electrode Fz. For GBS, positive memantine effects would be detected by increased 40 Hz evoked power at electrode Fz. Unlike those for PPI, predictions of positive memantine effects on MMN and GBS are not based directly on previous findings from our laboratory, using measures identical to those proposed herein. However, based on reports in healthy subjects from other laboratories of memantine effects on MMN (d=0.87) and ketamine effects on GBS (d=0.69), the proposed 30 patients/dose group would yield power of 0.90 and 0.75, respectively, to detect positive memantine effects on these measures.

10. HUMAN SUBJECTS

The subject population will include normal controls and individuals with existing diagnoses of schizophrenia. Men and women will be represented and ethnic representation in the sample groups will be determined by recruitment responses. Exclusion criteria for control subjects are psychiatric disorders in self or first degree relative, organic brain dysfunction, pregnancy or history of substance abuse. Psychiatric subject exclusion criteria are serious medical or neurologic illness, history of seizures, sustained loss of consciousness, substance abuse/dependence or pregnancy.

The drug evaluation studies will include normal subjects and individuals with existing diagnoses of schizophrenia. They will range in age from 18-35 years for all studies except those involving memantine, in which case they will range from 18-45 years. Males and females will be included in future studies. Subjects will be given a complete screening physical exam and will be excluded if showing any evidence of cardiovascular disease (e.g., hypertension, arrhythmia). Control subjects will also be screened for evidence of psychopathology or history of substance abuse using a modified SCID-N interview. If either is evident, the subject will be excluded from the study. All subjects will be informed of the nature of the study by a research assistant who will obtain consent if the subject wishes to participate. All subjects will be mentally competent and capable of giving informed consent.

Table 3. Proposed samples for ongoing / planned studies:

Study	Population	Total Sample	Rate	Status
"ONE-DAY" parametric studies	Normal Controls	up to 50/yr	50/yr	as needed
"WITHIN-SUBJECT" amphetamine/COMT	Normal Controls	120	60/yr	ongoing
"WITHIN-SUBJECT" memantine	Normal Controls	30	30/yr	ongoing
"WITHIN-SUBJECT" memantine	schizophrenia	60	24/yr	planned

The proposed study samples (Table 3) reflect both logistical and power consideration (see above, section "8. j. Statistics.") that differ across the several different studies covered by this application. Testing in the "ONE-DAY" session is designed for parametric "mini-studies", and the proposed sample of "up to 50 subjects" per year will allow us to study up to 5 different sets of stimulus parameters, with n's of 10 subjects per study. To study drug effects on PPI in normal control subjects, our target samples have historically been 20-30 subjects per dose; however, with the addition of COMT subgroup analyses, we currently plan to test 120 subjects in the within-subject amphetamine study, over a 2 year period (n=60/year). To study the effects of memantine on PPI and related measures in schizophrenia patients, we are proposing to study a total of 60 subjects: 30 per dose (10 and 20 mg). As this testing will be conducted over 2 - 3 years, we estimate recruitment needs of approximately 2 subjects per month, which will be easily accommodated by our recruitment capacity at the UCSD Medical Center, based on experience over the past 25 years.

Records and data will be rigorously protected, as described below. Aside from historical and questionnaire data, startle response, negative priming, MCCB, mismatch negativity and gamma band synchronization data will be obtained. Urine will be obtained for toxicological analysis as part of the subject exclusion process. Blood samples will be collected to identify genes that may be associated with PPI or its sensitivity to drugs.

The ethnic population in our male studies from the last 5 years (as we've only studied males exclusively based on drug study exclusion criteria) and is expected in the following years are:

Asian/Pacific Islander	29%
Black (not Hispanic)	3%
Hispanic	10%
White (not Hispanic)	56%
Other/unknown	2%

The ethnic population in our non-drug female studies from the last 5 years and is expected in the following years are:

Asian/Pacific Islander	12.5%
Black (not Hispanic)	2.5%
Hispanic	8.75%
White (not Hispanic)	72.5%
Other/unknown	3.75%

These numbers reflect the location of where we typically recruit subjects.

11. RECRUITMENT

1) Control subjects: Recruitment of clinically normal control subjects will follow our established and successful methods, using public announcements (e.g., newspapers and bulletin boards, online advertisements). Fliers that are posted and faxes that are sent to the UCSD Guardian (on-campus newspaper) are enclosed. Phone screening excludes subjects with a history of serious medical or neurologic illness or trauma, mental illness (including substance abuse), psychotropic medication use, known or suspected pregnancy or hearing problems. Screening is repeated at the time of testing, and a urine sample is collected for toxicological analysis (exclusion for illicit substances). The SCID is used with our published criteria to exclude theoretically "psychosis-prone" control subjects, important for

comparisons with schizophrenia patients. A handedness questionnaire is used to distinguish right and left handed subjects and a questionnaire for evaluating sexual preference is used to identify gender orientation, an important control in studies of sexual dimorphism of sensorimotor gating. Subjects also fill out cognitive and personality questionnaires: the Eysenck Personality Questionnaire (EPQ), Tridimensional Personality Questionnaire (TPQ), the Sensation Seeking Scale - Form V (SSS-V).

2) Schizophrenia patients: Recruitment of schizophrenia subjects will follow our established and successful methods. Patients will be recruited from the UCSD Outpatient Clinic, the UCSD VAMC clinics or community hospitals, and board and care facilities. Clinical assessment of schizophrenia patients follows our established procedures approved by the UCSD IRB for existing protocols (e.g. #071128, Dr. Greg Light, PI; #071306, Dr. Elizabeth Twamley, PI). Specifically, after giving informed consent, some schizophrenia patients will be interviewed using the SCID-I/P to ensure that they meet the DSM-IV criteria for schizophrenia. Demographic information, including age, age of onset, duration of illness, number and duration of hospitalizations, socioeconomic status, education, a detailed medication history, medical and psychiatric history, and family history of schizophrenia disorders will be obtained. Positive and negative symptoms of schizophrenia will be assessed during the Schedule for the Assessment of Positive Symptoms (SAPS) and Schedule for the Assessment of Negative Symptoms (SANS). Inclusion criteria include: 1) DSM-IV diagnosis of schizophrenia; 2) Written informed consent to participate in the study; 3) Age $\geq$ 18; 4) Absence of dementia or mental retardation; 5) Urine toxicology negative for recreational drugs; 6) Fluent and literate in English (needed for completion of MCCB). Exclusion criteria include: a) meets DSM-IV criteria for current substance abuse or dependence and has been substance abstinent for less than 30 days; b) a history of traumatic brain injury; c) auditory or visual impairments severe enough to prevent study participation.

Recruitment of female subjects: As per NIH guidelines, it is important to establish whether observed drug effects on these psychophysiological measures are sex-specific. Our current NIMH application thus proposes the use of female subjects in within-subject studies of drug effects on PPI, LI and related measures. At present, approval for studies in females is sought only for studies with amphetamine and memantine. Methods for these studies will be identical to those described above for male subjects, with the following exceptions: 1) urine pregnancy tests ("Surecheck Early Pregnancy Test") will be completed at the time of initial screening and test day 2 (exclusion: positive test); 2) testing will occur only during post-menses days 1-10; 3) blood will be drawn on the morning of testing and stored for possible later hormonal analyses using the GCRC/CTRI laboratory services; a total of 5 cc will be collected by venopuncture using GCRC/CTRI or hospital phlebotomy services.

12. INFORMED CONSENT

Recruitment of subjects and informed consent procedures will follow Dr. Swerdlow's established methods. For all subjects we will have a consent form indicating any or all of the following procedures to be used: startle gating, mismatch negativity, gamma band synchronization, MCCB, negative priming and latent inhibition. Subjects included in drug studies will be told of any potential side effects they may expect from the drug to be used during testing. Specifically, all subjects will be asked to read a description of the test drug, modified from the Physician's Desk Reference, which includes the following information: 1) the typical indications for this drug; 2) the recommended starting dose for this drug, and details regarding typical maintenance doses and schedules; 3) common side effects experienced by individuals taking this drug, based on trials with the indicated clinical population; and 4) an assessment of the likelihood that they will experience significant side effects from this drug, in the doses to be used in this study. In all cases, fully informed consent will be obtained and Dr. Swerdlow will be directly available to clarify any questions raised by a subject. Signed and witnessed consents will be kept on file with other patient data. The UCSD IRB has authorized no waivers or modifications of normal procedures.

Subjects will be carefully screened to ensure their ability to comprehend study procedures, risks, and benefits. Potential participants will be fully informed of all risks and benefits prior to giving their written informed consent and prior to enrollment in the study. Participants will be asked to repeat back understanding of this material, and if there is any question as to whether a person is able to provide informed consent then they will not be permitted to participate. A copy of the signed consent form will be stored in a separate locked filing cabinet from other de-identified coded materials, and a copy will be given to the study participant.

All study personnel involved in obtaining written informed consent will have completed a web-based course with post-test on Human Subject Research Protections and Good Clinical Practice, in addition to being trained by the Principal Investigator (PI) on obtaining informed consent. These study personnel will also be authorized to obtain informed consent by the IRB and Human Studies Subcommittee. Informed consent will be documented using standardized IRB-approved forms. The forms will be presented to all potential participants at the initial visit. Briefly, the informed consent form will describe the purpose of the study, procedures and participant involvement, nature of assessments and treatments, potential risks, alternatives to participation, costs and compensation, confidentiality, right to withdraw, potential benefits, relevant contact personnel, and information regarding the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Because participation in the proposed study is entirely voluntary, patients can choose to discontinue the study at any point for any reason and this will in no way affect future medical treatment decisions or practices.

Genetic Testing, Material & Storage: One goal of this proposal is to identify single nucleotide polymorphisms associated with differential sensitivity to drug effects on sensorimotor gating and neurocognition in clinically normal and schizophrenia subjects. To accomplish this, blood samples will be sought from all subjects by venopuncture at the UCSD Medical Center. Five ml (less than half of a tablespoon) of blood will be collected. DNA will be extracted by the Genomics Core Laboratory at UCSD. Tubes will be stored in a -80 degree freezer located at the CTF room A-310. All samples will be identified only by their subject ID to ensure confidentiality.

Subjects will be fully informed of the risks involved in providing a sample for DNA testing. Subjects will be told that Dr. Swerdlow will be responsible for how the blood specimen is used and that the specimens collected from the subjects and the DNA that they contain may also be used in additional research by Dr. Swerdlow. However, neither the blood, DNA nor information that identifies the subject will be shared with any other entity or collaborator or other party outside of our immediate research lab at UCSD. It will not be shared with any member of their family. Subjects will also be told that none of the results of their genetic tests could provide meaningful information related to their likelihood of developing or transmitting any specific disorder or medical condition. Results of the research that are specific to the subject will not be shared with anyone whether they have authorized it or not. If any publication results, the subject's name will not be used.

13. ALTERNATIVES TO STUDY PARTICIPATION

As stated in the current consent form, the alternative to study participation is to withdraw from the study.

14. POTENTIAL RISKS

Potential risks are minimal. The rating scales and questionnaires are innocuous. Startle testing exposes subjects to the application of skin tape electrodes and to brief loud sounds, which in >30 years of testing in the Braff and Swerdlow laboratories has caused no side effects. All other measures require only computer keyboard use and involve no risk. The cumulative risks of this proposal are judged as small. Below is a summary of the language in the consents.

1. An alcohol swab is used to clean the skin before electrodes are applied and some minor skin irritation and redness may occur.
2. Some participants might experience fatigue, boredom or irritation during the test session.
3. Some participants may be embarrassed or feel uncomfortable by some of the questions asked in the questionnaires.
4. Eyeblink startle exposes subjects to the application of skin tape electrodes and to brief loud sounds, which in our experience has caused no side effects.
5. During the study, your blood pressure and pulse will be regularly monitored.
6. Blood drawing may cause a small amount of pain. In addition, a temporary bruise or "black and blue mark" may develop. Rarely, people faint after having their blood drawn. Very rarely, the vein in which the needle has been inserted may become inflamed or infected, which can be treated.

For the drug evaluation study, the proposed drugs carry a very small risk of toxicity or adverse side effects in the doses to be used in this study. The most common side effects associated with each drug are listed in Section 8 above, and typically include nausea, somnolence and dizziness. We do not plan to administer these drugs to subjects in whom it is contraindicated, such as subjects with known cardiovascular or neurological disorders. The doses selected for use in these studies are in the low- or below-therapeutic range for these drugs when they are used clinically, and in most cases, the selected dose is equal to or less than the lowest recommended starting clinical dose for the drug. To address the potential for some of these drugs to produce changes in blood pressure, we will carefully monitor subjects' vital signs, and will not release subjects from the hospital until their vital signs are within normal limits. To address the possible side effect of somnolence, we will instruct subjects to arrange for their transportation from the hospital on test days. For studies that include women of childbearing potential, there is the possibility of unforeseen harm to an unborn child due to the administration of drugs. To address this risk, all female subjects will be asked to provide a urine sample to test for pregnancy and we will exclude participants who test positive. Additionally, all female subjects in these studies will be required to use a non-drug birth control method, such as abstinence, diaphragm, non-hormone intrauterine device to prevent pregnancy during the study. Subjects will be told to report if their menstrual cycle is inconsistent or if suspect that they are pregnant. Drugs will be dispensed by a licensed physician, and a licensed physician will be present on the premises at all times during testing. The consent forms include the related risks specific to the drug it refers to.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

The overall risks of this proposal are small. Protection of subject confidentiality and privacy will be rigorously guarded by the assignment of coded numbers to each file in the computer analysis and database. Resulting data will not be released to any subject, and released only to a patient's primary physician when an appropriate release form is signed by the patient. The UCSD psychophysiology research laboratory of Dr. Swerdlow has studied over 1000 control subjects and patients without any problems with confidentiality.

For the drug evaluation study, risk management procedures include: 1) Subjects will be asked to refrain from alcohol or other drug use while on the study. 2) Each subject will receive a complete history and physical examination prior to acceptance into the study. 3) A battery of psychological tests will be administered, as will an EKG and urine toxicology screen (which will also be used to test for pregnancy in drug studies including women of childbearing potential). 4) Subjects involved in studies with drugs will arrange for their transportation from the hospital, and any subject reporting any sedation upon completion of the study will be instructed to not operate a motor vehicle until the sedation is resolved. Subjects known or determined to have cardiovascular disease by EKG or patient history will be excluded. All subject information will be kept in a secure and locked area of the laboratory, CTF Building, UCSD Medical Center. Confidentiality will be protected to the extent provided by law.

If a participant has any questions regarding the study, they may contact the PI, Neal Swerdlow, M.D., Ph.D., Monday-Friday, 8 a.m. – 4:30 p.m. at (619) 543-6270. He may be reached after hours by contacting the UCSD operator at (619) 543-6222 and having them page Dr. Swerdlow. If any emergencies arise related to participating in these studies, the participant may proceed to the nearest emergency room or call 9-1-1.

Subjects will be told that they can terminate the experiment at any time if an aspect of the procedure causes them discomfort.

Risks associated with specific study populations: Because the proposed studies include schizophrenia patients, it is important to consider any risks that might be specifically elevated in this study population. As noted above, clinical trials with schizophrenia patients in which daily dosing of 10 - 20 mg memantine was added to ongoing medications have generally reported no or minimal evidence of either clinical improvement or adverse events. Thus, the likelihood that a single pill of 10 - 20 mg memantine would be associated with clinical changes is low. The population of schizophrenia patients to be enrolled in these studies will come primarily or exclusively from subjects who are seeking enrollment in an existing protocol

for supported employment (#071306, Dr. Elizabeth Twamley, PI); based on this, they will most likely be high functioning, clinically stable, and (by definition) seeking employment. Nonetheless, should the subjects voice any thoughts of self-harm or suicidality, all testing staff are instructed to immediately contact the licensed physician who is on-site and covering each test session. The physician will then immediately evaluate the subject, and based on their clinical condition, might escort them across the street to the Emergency Room at the UCSD Medical Center for further evaluation and, if necessary, treatment. It is important to note that, in over 30 years of testing schizophrenia patients at the CTF in the laboratories of Drs. Swerdlow and Braff, including several thousand schizophrenia patients and several drug challenge studies, only 1 subject has ever required an escort to the UCSDMC Emergency Room.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

All data and specimens are de-identified, and coded numbers are assigned to each file in the computer analysis and database. Research records are kept in a room separate from the data and specimens. Both the separate room and the filing cabinet containing the records are locked. Only the study coordinator has the key to access the files. Subject unique identifiers (name, DOB, SS#, etc.) will never be connected with the de-identified data. When published, data will remain de-identified, though subjects' non-unique demographic information (age, sex, ethnicity, handedness, diagnosis) may be reported together with the de-identified data. No other information will be provided to entities beyond the PI and key personnel noted in this application. The PI's UCSD research laboratory has studied over 1000 subjects and patients without any problems with confidentiality.

Positive drug screen results, if they became known outside the research, could reasonably place the subject at risk of criminal civil liability or be damaging to the subject's financial standing or employability. There is also the possibility of loss of confidentiality. Research records will be kept confidential to the extent allowed by the law. A study number will be used to identify information from participants. The database that relates the participants to a specific study number will be maintained using initials. Any database file will be encrypted on a password-protected computer.

All recruitment, interviewing, consenting, physical examinations and testing will take place in a private setting, specifically a dedicated interview room at the UCSD Medical Center, occupied only by the interviewing staff, physician and test subject, with the door closed, and a "DO NOT DISTURB" sign posted on the door.

It is NOT reasonably foreseeable that the study will collect information that Federal, State, and/or local laws/regulations requires to be reported to other officials (e.g., child or elder abuse; positive results from lab tests). However, as is true of any clinical population, and particularly in patients with brain disorders, it is possible that subjects may exhibit severe psychiatric symptoms including the description of suicidal ideation. An on-call licensed physician is covering all studies; should any such clinical issues arise, the covering physician will be contacted and will assess the situation for the most appropriate clinical intervention.

17. POTENTIAL BENEFITS

The information gained in these studies is expected to lead directly to a greater understanding of the pathophysiology of serious illnesses, and will facilitate the development of novel treatment strategies.
For the drug evaluation study, those likely to benefit most from the proposed project are severely ill psychiatric patients, as enhanced understanding of their cognitive and neurochemical abnormalities will allow for more accurate assessment and treatment of their symptoms. Individual subjects will benefit from a medical and psychological evaluation. Control subjects are unlikely to receive any other direct benefits from the proposed study other than the opportunity to contribute to efforts designed to relieve human suffering; there is evidence that participation in generative activities that improve self-esteem can have a positive impact on an individual's quality of life. Individuals with schizophrenia may or may not benefit from the long term goal of their study: to identify medications that will enhance the clinical impact of cognitive interventions in psychiatric patients.

18. RISK/BENEFIT RATIO

For the drug evaluation study, the risks from study participation include mild discomfort from drug effects, and the benefits include careful medical evaluation and potential gains in self-esteem among study participants, and significant benefit to patients in terms of knowledge gained related to the nature and optimal treatments of psychiatric disorders. The risk-benefit ratio of this study is very low.

19. EXPENSE TO PARTICIPANT

N/A

20. COMPENSATION FOR PARTICIPATION

The subjects will be paid $30 for the SCREENING SESSION and $130 for completion of the TEST SESSION. These payments have been accepted by the Human Subjects Committee as reasonable amounts for the length of subject participation. Subjects that participate in the "WITHIN-SUBJECT" study will be paid $30 for the SCREENING SESSION, $100 after the first test day and $130 for the completion of the second test day. This is a total of $260. Subjects will be reimbursed for parking costs on the SCREENING and TEST days and given breakfast and lunch on the TEST day.

Participants in the ONE-DAY study will be paid a total of $30. Compensation will be prorated to $10 per hour if the following happens: participants do not pass the tests; participants voluntarily withdraw from the study; or study personnel withdraw participants from the study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

The PI, Neal Swerdlow, M.D., Ph.D., is a licensed physician and Board Certified Psychiatrist. Co-investigators, Drs. Greg Light and Elizabeth Twamley, are licensed Clinical Psychologists. The Human Subjects Coordinator, Jo Talledo, has a BA in psychology and along with the PI analyze data collected from psychiatric and control subjects. Dr. Swerdlow and Ms. Talledo are trained to test psychiatric and control subjects with the described psychophysiological procedures, Reza Farokhpay, M.D. is a licensed physician. Susrutha Thanam, M.D., Samantha Hines (student) and Sarah Lamb (BA in psychology) are short term volunteers and employees who will be trained by Dr. Swerdlow and Ms. Talledo to become Laboratory Technicians. Maria Bongiovanni will assist in administrative issues.

22. BIBLIOGRAPHY

- Alessi SM, Greenwald M, Johanson CE. The prediction of individual differences in response to D-amphetamine in healthy adults. Behav Pharmacol. 2003 Feb;14(1):19-32.
- Bitsios et al. Increased prepulse inhibition of the acoustic startle response is associated with better strategy formation and execution times in healthy males. Neuropsychologia 44:2494-9, 2006.
- Giakoumaki et al. Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. Neuropsychopharmacol 33:3058-68, 2008.
- Giakoumaki et al. The level of prepulse inhibition in healthy individuals may index cortical modulation of early information processing. Brain Res 1078:168-70, 2006.
- Hutchison KE, Wood MD, Swift R. Personality factors moderate subjective and psychophysiological responses to d-amphetamine in humans. Exp Clin Psychopharmacol. 1999 Nov;7(4):493-501.
- Light et al. Prepulse inhibition of startle is positively associated with higher order cognition in women. Abstr, Soc Neuroscience 806.17, 2007.
- Mattay et al. Catechol 0-methyltransferase val158-Met genotype and individual variations in the brain response to amphetamine. PNAS 100: 6186-6191, 2003.
- Roussos et al. Prepulse inhibition of the startle reflex depends on the catechol O-methyltransferase Val158Met gene polymorphism. Psychol Med 38:1651-8, 2008.
- Swerdlow et al. The effects of memantine on prepulse inhibition. Neuropsychopharmacol 34:1854-64, 2009.
- Swerdlow NR et al. Antipsychotic effects on prepulse inhibition in normal 'low gating' humans and rats. Neuropsychopharmacology. 2006 Sep;31(9):2011-21.
- Swerdlow NR et al. Amphetamine effects on prepulse inhibition across-species: replication and parametric extension.
- Swerdlow NR et al. Effects of amantadine and bromocriptine on startle and sensorimotor gating: parametric studies and cross-species comparisons. Psychopharmacology (Berl). 2002 Oct;164(1):82-92.

- Swerdlow NR et al. Effects of amantadine and bromocriptine on startle and sensorimotor gating: parametric studies and cross-species comparisons. Psychopharmacology (Berl). 2002 Oct;164(1):82-92.
- Swerdlow NR et al. Pramipexole effects on startle gating in rats and normal men. Psychopharmacology (Berl). 2009 Sep;205(4):689-98.
- Talledo et al. Amphetamine effects on startle gating in normal women and female rats. Psychopharm 204:165-75, 2009.
- White TL, Lejuez CW, de Wit H. Personality and gender differences in effects of d-amphetamine on risk taking. Exp Clin Psychopharmacol. 2007 Dec;15(6):599-609.

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- NIDA 5R03 DA027483-02 (PI) 9/1/09 – 8/31/11
- NIMH R01 MH059803 (PI) 12/7/2010 – 11/30/2013

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

NA

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

NA

26. IMPACT ON STAFF

NA

27. CONFLICT OF INTEREST

NA

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

NA

29. OTHER APPROVALS/REGULATED MATERIALS

NA

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Schizphrenia patients who have been identified for participation in our studies will also be enrolled in IRB-approved clinical trials of cognitive training with Dr. Twamley. Dr. Twamley has approval to screen and administer surrogate identification process. Any patients that have been identified as having impairment in their decision-making ability will be determined by Dr. Twamley and will not be referred to our studies.

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