Protocol Title: Dopamine Receptor Imaging to Predict Response to Stimulant Therapy in Chronic TBI
Abbreviated Title: Dopamine Receptor Imaging in TBI
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Total requested accrual
(30) Patients
(0) Healthy Volunteers

Project Uses Ionizing Radiation: ☐ No X Yes (*attach RSC/RDRC documentation)*
☐☐ Medically indicated only
XResearch-related only
☐☐ Both

IND/IDE ☐ No X Yes *(attach FDA documentation)*
Drug/Device/#___ [11C]-raclopride N 54,135.
Sponsor: Herscovitch, Peter, MD

Durable Power of Attorney X No ☐ Yes

Multi-institutional Project X No ☐ Yes
Institution#1_____ FWA #_____
Date of IRB approval _____*(attach IRB documentation)*

Institution#2_____ FWA #_____
Date of IRB approval _____*(attach IRB documentation)*

Data and Safety Monitoring Board X No Yes

Technology Transfer Agreement ☐ No X Yes
Agreement type and number _In progress__ Expiration Date_____

Samples are being stored ☐ No X Yes

Flesch-Kincaid reading level of consent form: ____9_____

Précis

***Objectives*:** Deficits in memory, attention, cognitive, and executive functions are the most common disabilities after traumatic brain injury (TBI). Dopamine (DA) neurotransmission is implicated in these neural functions and dopaminergic pathways are recognized to be frequently disrupted after TBI. One of the most widely used DAergic drugs is methylphenidate (Ritalin®). Methylphenidate increases synaptic DA levels by binding to presynaptic dopamine transporters (DAT) and blocking re-uptake. PET with methylphenidate challenge to measure tonic DA release provides valuable insight into the molecular basis of attention-deficit hyperactivity disorder (ADHD) and addiction, as well as practical information regarding likely effectiveness of therapy [1]. The objectives of this study are to use PET imaging with [^{11}C]-raclopride, a D2/D3 receptor ligand, before and after administering methylphenidate, to measure endogenous DA release in patients who are experiencing problems with cognition, attention and executive function in the chronic stage after TBI. In addition, we will use TMS to test short intracortical inhibition, a gamma-aminobutyric acid receptor A ($GABA_A$) - mediated phenomenon, which is under partial DA control, as a measure of dopaminergic activity on and off methylphenidate.

Study population: Males and females (n=30), between the ages of 18 and 55 years in the chronic stage after TBI who experience deficits in neuropsychological function from TBIs incurred 6 months after the injury, will be recruited from military treatment facilities or civilian clinics when presenting for clinical management of TBI or post-concussive symptoms.

Design:
1. Study participants will be evaluated using brain MRI, psychometric measures adapted from the TBI Common Data Elements, attention tests and information about details of the injury and experience of post-concussive symptoms will be recorded. Transcranial magnetic stimulation (TMS) with placebo and with methylphenidate (60 mg by mouth) challenge will be performed to predict a stimulant response.
2. Subjects will be studied with [^{11}C]-raclopride PET in two imaging sessions. One session will be after administration of placebo and the other after methylphenidate, 60 mg by mouth. Both placebo and methylphenidate will be given 60 minutes prior to injection of [^{11}C]-raclopride to allow for peak uptake of methylphenidate in the brain. The binding potential of [^{11}C]-raclopride relative to a non-displaceable reference region (cerebellum), BP_{ND}, will be used as a measure of D2/D3 receptor availability. The difference in BP_{ND} between methylphenidate and placebo (ΔBP_{ND}) is used to measure of tonic DA release.
3. Subjects will then be treated with oral methylphenidate, using a forced titration up to a dose of 30 mg given twice daily for 4 weeks. At that point, the neuropsychologic tests are repeated.

***Outcome measures**:* The primary outcome is change in information processing speed during neuropsychologic testing.

Contents

List of Abbreviations

ADC	Apparent Diffusion Coefficient
BBB	Blood Brain Barrier
BSI	Brief Symptom Inventory
BMI	Body Mass Index
CBF	Cerebral Blood Flow
CDE	Common Data Elements
CLIA	Clinical Laboratory Improvement Amendments
CNRM	Center for Neuroscience and Regenerative Medicine
CNS	Central Nervous System
CTE	Chronic Traumatic Encephalopathy
CVLT	California Verbal Learning Test
CVLT-II	California Verbal Learning Test – 2nd Edition
D2R	Dopamine 2 receptor
DA	Dopamine
DAT	Dopamine transporter
DMN	Default mode network
DOD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EMG	Electromyogram
FA	Fractional Anisotropy
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
FWA	Federal Wide Assurance
GCS	Glasgow Coma Score
GABAA	Gamma-aminobutyric acid
GOS-E	Glasgow Outcome Score – Extended
GUID	Global Unique Identifier
IND	Investigational New Drug
IRB	Institutional Review Board
MEP	Motor evoked potential
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
MTT	Mean Transit Time
NiCOE	National Intrepid Center of Excellence
NIH CC	National Institutes of Health Clinical Center
NINDS	National Institutes of Neurological Disorders and Stroke

NSI	Neurobehavioral Symptom Inventory
PET	Positron Emission Tomography
PFC	Prefrontal cortex
PWI	Perfusion Weighted Imaging
rfcMRI	Resting state functional connectivity MRI
SICI	Short interval intracortical inhibition
SPECT	Single photon emission computerized tomography
SWI	Susceptibility Weighted Imaging
SWLS	Satisfaction with Life Scale
TBI	Traumatic Brain Injury
TMS	Transcranial magnetic stimulation
TTP	Time to Peak
USUHS	Uniformed Services University of the Health Sciences
VA	Veterans Affairs
VS	Ventricular striatum
WRAT	Wide Range Achievement Test
WRNMMC	Walter Reed National Military Medical Center

1. Introduction

Background/Preliminary Data: Dopaminergic pathways are recognized to be frequently disrupted after TBI. In humans, there are three major dopaminergic fiber systems, all of which share the basic organization of cell bodies located in midline structures and long projection neurons innervating widespread cortical and subcortical regions (Fig 1). Because of the organization of DA pathways, they are susceptible to shearing and rotational forces common in TBI.

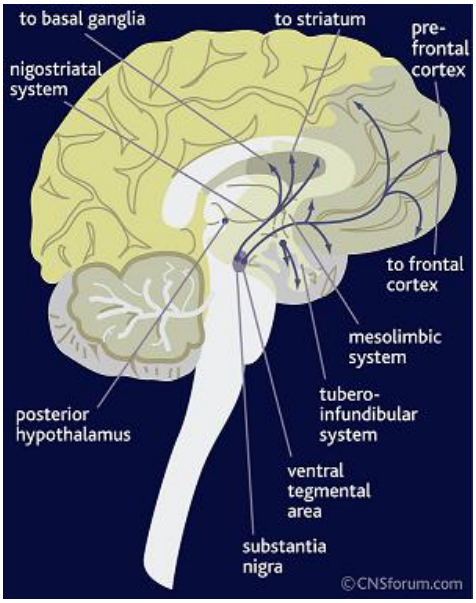

Fig 1. Dopaminergic Pathway in human brain. The *nigrostriatal DA system* has cell bodies in the substantia nigra pars compacta in the ventral midbrain, and project to the caudate and putamen, referred collectively as the neostriatum. The nigrostriatal pathway is important for regulating motor control and learning motor programs and habits. The *mesolimbocortical DA system* has cell bodies in the ventral tegmental area, just medial and posterior to the substantia nigra, and projects to limbic and cortical structures, such as the nucleus accumbens, prefrontal cortex, and cingulate cortex. The mesolimbocortical pathway regulates both cognitive and emotive functions, and plays a major role in the reward pathway. Finally, the *tuberoinfundibular DA system* has cell bodies in the arcuate nucleus of the ventral hypothalamus and projects to the median eminence, where it plays an important role in regulating hormone release from the anterior pituitary.

1. *Evidence that DA pathways are damaged after TBI.*

There is evidence to suggest that DA pathways are often disrupted as a result of trauma [2]. First, patients with TBI frequently have problems with attention, concentration, processing speed, executive function, fatigue, and memory, functions that are recognized to involve DA pathways. Second, brain regions such as the prefrontal cortex, limbic structures and striatum, which are known to be rich in DA innervation, are frequently injured after TBI [3, 4]. Finally, a series of reports and small studies dating back 25 years indicate that neurostimulants working on the DA system are beneficial in improving cognitive and attentional deficits after TBI. This evidence is reviewed below (Table 1) in more detail regarding methylphenidate, but similar data exist for amphetamine, amantadine, and bromocriptine (reviewed in detail by Bales et al.) [2].

Direct (but limited) evidence of dopaminergic dysfunction after TBI comes from SPECT studies using radioligands that bind the presynaptic DA transporter (DAT) and the DA D2 receptor (D2R). Donnemiller et al. [5] used ^{123}I-β-CIT to label DAT and ^{123}I-IBZM to image DR2 in 10 patients with primarily severe TBI 4-5 months after injury. Compared with age-matched controls, patients with TBI had significantly lower ^{123}I-β-

CIT and ^{123}I-IBZM binding in the striatum. This was found even in cases with no anatomical evidence of direct striatal injury. Despite the increased availability of PET and SPECT ligands for both the pre- and postsynaptic DA system, this study, published over 10 years ago, remains the only one to directly image the DA system after TBI.

2. Evidence that drugs working on the DAergic system are useful after TBI.

There have been multiple attempts over the last two decades pharmacologically manipulate the DA systems to improve functional outcome. Neuropharmacologic therapies are commonly used off label to enhance arousal and behavioral responsiveness, on the premise that injury-induced derangements in dopaminergic and noradrenergic neurotransmitter systems can be improved through supplementation. Amantadine hydrochloride is one of the most commonly prescribed medications for patients with disorders of consciousness who are undergoing inpatient neurorehabilitation [6]. Recently, Giacino et al. [7] conducted a multicenter trial of 184 patients who were in a vegetative or minimally conscious state 4 to 16 weeks after TBI and who were receiving inpatient rehabilitation. During the 4-week treatment period, recovery was significantly faster in the amantadine group than in the placebo group, indicating a benefit with respect to the primary outcome measure. This study was the first ever Class I randomized controlled trial which shows the benefit of a pharmacologic agent after TBI.

Methylphenidate is another drug acting on DA neurotransmission commonly used off label by physiatrists attempting to improve recovery after TBI. It acts by blocking catecholamine reuptake DA and norepinephrine (NE) levels in the synapse. **Table 1** summarizes the published data on cognitive outcomes using methylphenidate in TBI (adapted from Bales [2]). Most studies focused on the chronic stage after TBI.

Table 1. Cognitive outcomes with the use of methylphenidate in TBI

Citation	n	Phase treatment administered	Cognitive Outcomes Measured	Conclusion
Gualtieri (1988)	15	Chronic	Memory, attention	Benefit in memory
Mooney and Haas (1993)	38	Chronic	Memory, attention, anger	Benefit in memory
Speech et al (1993)	12	Chronic	Attention, learning, cognitive processing	No significant effects
Kaelin et al (1996)	10	Subacute	Attention, Disability Rating Scale (DRS)	Improvement in recovery of attention
Plenger et al (1996)	23	Recovery	Attention, memory, diligence, DRS	Enhanced rate of recovery
Whyte et al (1997)	19	Chronic	Attention	Improvement in speed of mental processing
Whyte et al (1997)	10	Recovery-Chronic	Attention, memory, behavior, processing speed	No significant effects
Whyte et al (1997)	14	Recovery-Chronic	Attention	Improvement in attention and concentration
Whyte et al (2004)	34	Chronic	Attention	Improvements in speed of processing, caregiver ratings of attention
Kim et al (2006)	18	Chronic	Working memory,	Improvement in cognitive

			visuospatial attention	function, e.g., working memory reaction time
Lee et al (2005)	10	Subacute	Memory, attention	Improvement in cognitive function and maintaining daytime alertness
Pavslovskaya et al (2007)	6	Chronic	Visuospatial attention	Improvement in attentional shifts

Despite this body of largely consistent studies, methylphenidate is not considered standard of care in the treatment of disorders of cognition, attention, or behavior after TBI. Frenette et al. [8] published a systematic review of randomized controlled trials on the efficacy and safety of DA agonists in TBI. They concluded that significant clinical heterogeneity was observed between and within studies, which precluded any pooling of data. They stated that: "Considering the absence of consensus regarding clinical outcome, the lack of safety assessment, and the high risk of bias in the included trials, more research is warranted before DA can be recommended in TBI patients."

3. Imaging of pre- and post-synaptic DA markers is useful for assessing DAergic function in neuropsychiatric disease, and for predicting response to therapy.

Several radiotracers for positron emission tomography (PET) and SPECT were recently developed and successfully applied to assess the integrity of presynaptic DA neurons and postsynaptic DA receptors in humans. Of these, [^{11}C]-raclopride, a D2/D3 receptor ligand whose specific binding is sensitive to competition by endogenous DA, has been extensively

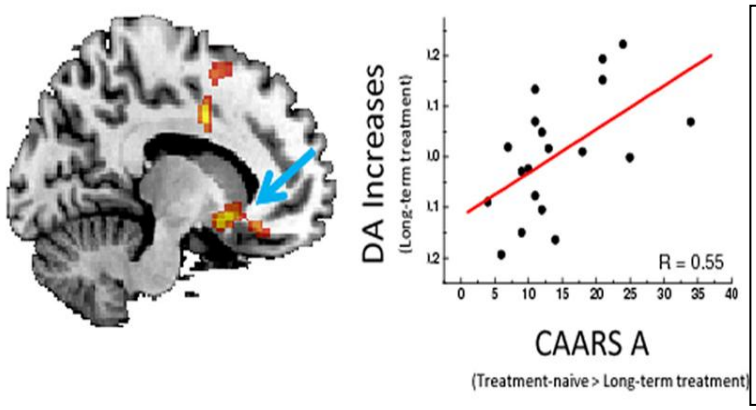

Fig 2. Impact of dopamine release subsequent to methylphenidate administration on outcome in adult patients with ADHD. Voxel-wise correlation between intravenous MP-induced changes in DA D2/D3 receptor availability in ventral striatum (measures taken after long-term MP treatment) and the improved scores of symptoms of inattention (CAARS A). (From Volkow et al 2012) [1]

used to indirectly assess DA release (Fig. 2) [1, 9-11]. This technique was used to identify deficits in DA circuitry in ADHD and addiction disorders, but was never used to assess cognitive and behavioral deficits after TBI. Dr. Volkow has pioneered these studies over the past 15 years [9, 11, 12], and Dr. Herscovitch has adapted them at the NIH PET Center in studies of alcohol dependence [10]. These methods are well established and their application to patients with neuropsychiatric disorders after TBI is a promising and timely application of this technique.

4. Functional connectivity of prefrontal cortex and DA receptor availability. Large-scale brain networks underlie many of the complex behaviors influenced by DA pathways,

including reward, executive function and addiction [13, 14]. Functional MRI (fMRI) in the resting state can identify functional brain networks such as the default mode network (DMN) which underlie complex behaviors such as cognitive control, salience processing, and reward-related brain activity. Recently, the functional connectivity of the orbitofrontal cortex in the DMN was associated with D3 receptor availability in the midbrain [15]. This observation provides the rationale for our proposal to investigate resting state functional networks, and to explore any changes in functional connectivity of the PFC as a result of methylphenidate therapy. The ability to assess the integrity of DAergic circuits with fMRI would have major clinical implications, since fMRI is a much more widely available technology compared to [^{11}C]-raclopride PET.

5. Transcranial magnetic stimulation (TMS) of motor cortex as a biomarker of integrity of DA circuits.

The motor cortex (M1) receives direct dopaminergic input [16] which inhibits corticospinal output neurons [17]. The response of the motor cortex to transcranial magnetic stimulation (TMS) is affected by DA agonists and antagonists [18] and amphetamine [19] in healthy subjects. Dr. Wassermann and colleagues measured the effect of methylphenidate and the specific NE reuptake inhibitor, atomoxetine, on the same measures in ADHD, where decreased M1 inhibition correlates with symptom severity [20, 21], suggesting deficient DA input. These medications both produced an increase in inhibition similar to that seen with DA agonists. We propose using the same TMS paradigm to measure M1 inhibition before and after administration of methylphenidate. Our expectation is that patients who respond to treatment behaviorally and with greater [^{11}C]-raclopride displacement on PET will show a greater increase in M1 inhibition on methylphenidate than those who do not. Ideally, TMS might be used to predict stimulant response.

5. Behavioral effect of methylphenidate on motivation and rewardability in TBI.

Fatigue and loss of motivation are frequently observed after TBI [22, 23], but are difficult to quantitate. This problem has been attributed to dysfunction in the dopaminergic reward system and there is a presumption that dopaminergic treatment can restore this function. We have designed and tested a quantitative way to measure the willingness of individuals to perform muscular contractions for different reward values and propose to use it here, on and off methylphenidate, as an exploratory measure of motivation and rewardability.

This study is sponsored by the Center for Neuroscience and Regenerative Medicine (CNRM). To address the profound issues related to the diagnosis and treatment of TBI, the United States Congress, through Public Law 110-252, established the Center for Neuroscience and Regenerative Medicine (CNRM) as a collaborative intramural program in May 2008. The Congressional Record of May 15, 2008, expressed Congressional intent that the CNRM study actual combat casualties cared for at Walter Reed Army Medical Center (WRAMC) and the National Naval Medical Center (NNMC) using advanced neuroimaging technology in collaboration with the National Institutes of Health (NIH).

2. Study objectives

Primary Objective:

To assess the relationship between tonic DA release (assessed by displacement of [^{11}C] raclopride by oral methylphenidate) and improvement in processing speed after 4 weeks of treatment with oral methylphenidate.

Secondary Objectives:

(1). Assess the relationship between D2/D3 receptor availability in the VS and PFC with neuropsychological deficits in the chronic stage after TBI.
(2). Assess the relationship between tonic DA release in the VS and PFC with neuropsychological deficits after TBI.
(3). Determine the relationship between D2/D3 receptor availability and functional connectivity of the PFC with nodes of the default mode network.
(4). Assess the relationship between TMS-induced short-interval cortical inhibition (SICI) of M1 and tonic DA release, as well as response to methylphenidate therapy.
(5). To test motivation and reward on and off methylphenidate in TBI patients.

Exploratory Objectives:
(6). Use diffusion tensor imaging (DTI) to explore the relationship between structural connectivity between the VS, PFC, and ventral tegmental area (VTA), and tonic DA release in patients in the chronic stage after TBI.

3. Subjects

a. Description of study populations

The study population includes male and female volunteers with TBI between the ages of 18 and 55 years. The accrual ceiling will be 30. Dropouts and loss to follow-up will be considered under intention-to-treat principles.

b. Inclusion criteria

To be included in the protocol, study participants must meet the following criteria:

1. Age 18 – 55 years, inclusive
2. A history of having sustained a moderate or severe TBI ≥ 6 months prior to enrollment. Evidence will be any **one** of the following 3 criteria:
   a) GCS 3 – 12 (GCS obtained in Emergency Room and noted in medical record)
   b) Post-traumatic amnesia > 24 hours
   c) TBI-related abnormality on neuroimaging (either CT or MRI).

   (Some missing information about the initial injury [i.e., documentation of initial GCS] is not necessarily exclusionary if the bulk of the available history indicates that the patient suffered a TBI and meets the inclusion criteria)
3. Persistent post-concussive symptoms, according to the DSM-IV Research Criteria for Post-Concussional Disorder, including:
   a) Difficulty in attention or memory.
   b) **One or more** of the following symptoms, which started shortly after the trauma and persist for at least three months:
      i) Fatigability
      ii) Disordered sleep
      iii) Changes in personality
      iv) Apathy or lack of spontaneity
   c) Symptoms in criteria (a) and (b) must have their onset after trauma, or there was a significant worsening of pre-existing symptoms after trauma.
   d) Disturbance from these symptoms causes significant impairment of social or occupational functioning and represents a significant decline from previous level of functioning.
4. Ability to read, write and speak English
5. Ability to give informed consent.

c. Exclusion criteria

1. Evidence of penetrating brain injury.
2. Contraindication to methylphenidate therapy:
    1. Known glaucoma (consistently raised intraocular pressure with or without associated optic nerve damage)
    2. Motor tics or a family history of Tourette's syndrome (diagnosed by presence of both multiple motor and one or more vocal tics over the period of a year, with no more than three consecutive tic-free months)
    3. Known hypersensitivity to methylphenidate (hives, difficulty breathing, and swelling of face, lips, tongue, or throat)
    4. Known severe anxiety or restlessness which prevents from doing day to day activities.
    5. Known preexisting hypertension, heart failure, myocardial infarction, or ventricular arrhythmia
    6. Known preexisting psychosis, bipolar illness
    7. History of seizures, or interictal epileptiform discharges (IEDs) on EEG in absence of seizures
    8. Known peripheral vasculopathy, including Raynaud's phenomenon
    9. History of drug dependence or alcoholism
    10. Concomitant treatment with coumadin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine)
    11. Concomitant therapy with monoamine oxidase inhibitors (such as Marplan (isocarboxazid), Nardil (phenelzine), Emsam (selegiline), and Parnate (tranylcypromine))
    12. Concomitant treatment with blood pressure medication (both for high and low blood pressure)
    13. Pregnancy
    14. Breastfeeding.

3. History or evidence of disabling pre-existing or co-existing disabling neurologic or psychiatric disorders not related to TBI, such as:
    1. Multiple sclerosis, pre- or co-existing
    2. Stroke (other than stroke at the time of TBI)
    3. Pre-existing disabling developmental disorder
    4. Pre-existing epilepsy
    5. Pre-existing major depressive disorder, aggressive behavior, hostility
    6. Pre-existing schizophrenia.

4. Contraindication to MRI scanning:
    1. Ferromagnetic metal in the cranial cavity or eye, e.g., aneurysm clip, implanted neural stimulator, cochlear implant, or ocular foreign body
    2. Implanted cardiac pacemaker or auto-defibrillator or pump
    3. Non-removable body piercing
    4. Claustrophobia
    5. Inability to lie supine for two hours.
5. Contraindication to TMS, such as metal in the cranial cavity or implanted electronic hardware.

6. Current participation in other interventional clinical trial.
7. Non-adherence to use of effective method of contraception for females of able to become pregnant for time from enrollment to the study until 2 weeks after completion of the study drug.
8. Present history of alcohol and substance abuse disorder determined by DSM-IV.
9. Body mass index (BMI) > 40.
10. NIH employees

4. Study Design and Methods

4.1 Study overview

Summary of study design: This is an open-labeled 4 week methylphenidate administration, 30 mg twice daily by mouth. Placebo and methylphenidate will also be administered as a single dose before one of the two PET and TMS sessions, in a single blinded manner (the participant will not know whether active drug or placebo was administered). PET imaging with [11C]-raclopride, a D2/D3 receptor ligand will be performed after administration of placebo or oral methylphenidate to measure endogenous DA release in TBI patients. Structural MRI will be performed before methylphenidate administration. TMS after placebo or methylphenidate will be performed to measure intracortical inhibition and dopaminergic activity. Neuropsychological tests will be performed before and after methylphenidate administration for 4 weeks. The participants will be individuals, who are experiencing chronic problems with fatigue, cognition, attention, and executive function after TBI.

Site location: NIH Clinical Center.

Length of participation in the study: Participants enrolled in the study will have four outpatient study visits during an approximate 2 - month timeframe. Visits last from three to five hours. The study includes a diagnostic phase and an interventional phase and consists of three diagnostic visits and one follow up visit.

4.2 Recruitment

Source of subjects and recruitment venues: Study participants will be recruited from Walter Reed National Military Medical Center, National Intrepid Center of Excellence, Ft. Belvoir Community Hospital , McGuire Veterans Administration Medical Center in Richmond, Virginia, other area Veterans Administration clinics, the NIH, and CNRM's Facebook website (Appendix C) and Twitter page (Appendix A).
They also may be recruited from among volunteers who participated in other CNRM studies who signed consent and indicated that they would like to be contacted by investigators of other CNRM studies.

How potential subjects will be approached: Recruitment materials may be distributed at educational presentations. The IRB-approved brochure (Appendix C) will be distributed with the permission of the clinics' administration or IRB where applicable. Same recruitment brochure will be used as Facebook advertisement (Appendix C).
One of the investigators or study coordinator named in the protocol may contact participants from other CNRM studies who consented to be contacted for other studies. Investigators from other CNRM studies in which volunteers consent to be contacted for other studies may also be given the telephone number or email address of the study contact. The study telephone number is on the front of the brochure and will be advertised on the CNRM website and twitter page. We will also employ the NIH Clinical Center and the CNRM Recruitment Core resources. They may refer patients who call the centers inquiring about TBI studies to our central study number. Otherwise it will be up to the participant to call the study number. Self-referral is also permitted.

Accrual Rate: We plan to enroll 30 participants over a 2-year period.
Pre-screening questions for recruiters: Pre-screening will be performed by the study coordinator, investigators, and research assistants over the telephone or in-person. If the potential subject is unfamiliar with the details of the study and time requirements, the prescreener will use the pre-screening Script (Appendix D) along with the Eligibility Checklist to determine preliminary eligibility."
The members of the research team who will be qualified to administer the Eligibility Checklist will have to complete a Good Clinical Practice course and the class, "Elements of a Successful Consent" offered by HSPU.

If the potential participant expresses interest in the study, the person doing the pre-screening will ask if they have time to answer a short questionnaire that would allow him/her to evaluate their eligibility and safety for inclusion into the study (Eligibility checklist, Appendix F).

If based on this interaction, it appears that the subject might meet the inclusion criteria for the study, an appointment will be scheduled for the patient to come to NIH. To prepare for this visit, the potential participant will be asked for his/her full name (first and last), address, telephone number, and date of birth to be entered into the Admissions and Travel and Vouchers program.

Research staff may ask for medical records (recent history, medication list, recent imaging and pertinent records related to the subject's recent injury) to further evaluate their eligibility for the study. The subjects may bring their own medical records when they come to NIH for testing. The data may be reviewed by the investigator before the initial clinic visit, and if it is clear that the patient does not meet the inclusion criteria, we will contact them and cancel their appointment. Data obtained in this manner may be used to refine our inclusion and exclusion criteria; however, it will not be used for any research purposes. We will send their medical records back to them if they do not meet criteria.

Identifying information will be destroyed within one week of learning about a potential participant's pre-screening failure.

4.3 Screening

Informed consent will be obtained before any study procedures

Study Eligibility Evaluation

Potential study participants will come to the NIH Clinical Center and will be greeted by a research staff member. Participants will be checked in to the Clinical Center at the Outpatient Neurology Center, 5th floor by a clinic nurse.

The subject will undergo the following procedures:

1) Informed Consent: One of the physician investigators will obtain consent before any research and screening procedures are conducted. The consent is written in language appropriate for the subject to comprehend. The study physician will discuss the study with the potential participant, review all parts of the consent form, answer questions about the study, give a copy of the consent form to the participant and ask them to review it, consider it, ask questions, and discuss it with friends or family. If the participant decides to sign the form, a copy will be given to them to take home. The study coordinator or research assistant may assist the physician in reviewing the consent form in detail and in collecting information from the patient in order to complete the case report forms.

2) Screening by physician and study coordinator or research assistant

As a Clinical Center requirement, an NIH staff nurse will take vital signs including pulse, temperature, blood pressure, and respiration rate. The nurse may record a list of the participant's current medications and a brief medical history. One of the study physicians will do a history and physical exam, including a neurological exam which will be entered into CRIS.

Screening includes:

a. Medical history including information about the traumatic brain injury
b. Interview with the study physician
c. Urine pregnancy test if applicable.
d. Physician's determination of participant eligibility for the study

Determination of Subject Eligibility: Subject's eligibility for the study will be documented using the Eligibility Checklist, which is based on the Inclusion/Exclusion criteria. The checklist should be reviewed with each potential participant prior to the subject's initial visit. Final determination of eligibility will be determined by the physician investigator, using the patient's medical records, medical history, and in-person interview. Medical history including history of TBI will be collected from all subjects to assist the physician in eligibility determination. If medical records are unavailable, data such as time of injury, loss of consciousness, and post traumatic amnesia, are to be summarized from interviews with the subject.

Urine Pregnancy Test: If applicable, the study participant will provide a urine pregnancy test required for screening women able to become pregnant, unless they have had a surgical procedure permanently preventing pregnancy. This is part of the eligibility requirement.

Enrolled or screen failed: If the patient is deemed eligible by the investigator, then she/he will begin the study procedures. If the patient is not eligible, she/he will be considered a screen failure and will not go through study procedures. Signed consent forms for screen failures will be maintained with study records in Dr. Wassermann's research office. The research records will be kept in locked cabinets and the office will be locked when not in use. Their contact information will not be kept.

Volunteers who fail the enrollment criteria for this study will be considered screening failures. Screening failures will be counted separately than those that drop out for other reasons. Subjects who come into the Clinical Center will sign a consent form before engaging in any study procedures. If they do not meet eligibility for the study, even though they have signed a consent form, they will be considered screening failures. Once a participant has met eligibility criteria and engaged in a study procedure and chooses not to participate in the protocol, are lost to follow-up, or voluntarily withdraw or are involuntarily withdrawn from the study by the investigator, they will be counted as drop-outs for statistical purposes.

Contraception: Sexually active women who are able to become pregnant must agree to use an effective method of contraception (birth control) from the time they enroll in the study until 2 weeks after they have completed taking the study drug, methylphenidate.

4.4 Study Procedures

Informed consent will be obtained before any study procedures. All evaluations and procedures are done only for research purposes. **Table 2** is a schedule of procedures for each study visit. While the stated target time points and assessment batteries will be attempted for subjects in this study, it is anticipated that some subjects will not be able to undergo all tests at all times and may refuse assessments. Procedures may be done in a different order after consent and determination of eligibility depending on Imaging Center, Phlebotomy Center, and neuropsychometrician's schedules and availability.

Table 2 : Study Schematic

Study Procedure	Visit 1, Diagnostic	Visit 2, Diagnostic	Visit 3, Diagnostic	Visit 4, Follow-up	Time for the procedures
1. Informed Consent	X				30 min
2. Inclusion/Exclusion Criteria	X				15 min
3. Pregnancy test	X	X	X	X	5 min
4. Examination and medical history by physician/Investigator	X				30 min
5. Blood draw for research biomarkers and DNA	X			X	15 min
6. Structural MRI; T1 MPRAGE, FLAIR, DTI, 3DTI-SPGR, rfcMRI, GRE, SWI,	X				45 min
7. fMRI and Resting Functional Connectivity	X			X	15 min
8. Neuropsychometric Common Data Elements		X		X	60 min
9. Attention tests		X		X	60 min
10. TMS and motivation tests before and after methylphenidate*		X			2 X 80 min
11. PET scans (x 2) after administration placebo and then after methylphenidate**			X		2 X 2 h
12. Dispensing study drug (methylphenidate)			X		5 min
13. Examination by physician and pill counting for compliance				X	20 min
14. Monitoring for adverse effects	X	X	X	X	15 min
Time	2 h 50 min	5 h	4 h 25 min	3 h 10 min	

* TMS and motivation tests with placebo or methylphenidate can be administered separately on visits #1 or #3
** PET with placebo or methylphenidate can be done on visits #1 or #2

4.4.1 History and Physical examination

Subjects who are eligible for the study will have a physical examination which includes a neurological examination and medical history review by a study physician. All TBI subjects evaluated by the study investigators will be asked for written permission if they require medical records data, including imaging, collected as part of their regular medical care for research purposes.

This physical examination is for research purposes only and does not replace any examination they may receive from their own physicians. The study physician will write orders for imaging procedures, biospecimen collection, and methylphenidate dispensing.

Incidental findings on brain imaging, laboratory evaluation or physical examination:
The physician will inform the patient about any finding that may require further evaluation or care. Evaluation or treatments of these conditions are not provided at NIH. If needed, the study physician will refer the patient to a health care provider. The study team may not inform the patient about minor abnormalities that do not have importance for their health or well-being.

4.4.2 Biospecimen Sample Collection

a. Urine sample: Prior to MRI or PET scanning or TMS, urine specimens will be collected from women able to become pregnant for pregnancy tests. A urine pregnancy test must be done within 24 hours prior to MRI or PET or TMS. Subjects who have a positive pregnancy test will not undergo MRI, PET or TMS and will be excluded from the study. Urine will not be stored.

b. Blood sample: Venous blood samples will be collected from study participants by a trained phlebotomist or nurse at the Clinical Center during Visits #1 and #4. Blood samples will be drawn for research purposes.

For research purposes during this study, approximately 25 ml (approximately 5 teaspoons) of blood will be collected from participants at Visits #1 and #4. A total of 50 ml (approximately 11 teaspoons) will be collected over the 4 weeks of the study.
No specific genetic tests will be performed under this protocol because the sample size of this study is not sufficient to perform these studies. Since the sample size of this study is relatively small, it is not possible to determine the type of genetic polymorphism which will be analyzed in the future. The specimens will be transferred to the CNRM Biorepository and will be combined with similar types of samples for future studies.

Results of genetic testing obtained at NIH are often preliminary and difficult to interpret because the testing is being done for research purposes only and the laboratories are not CLIA-certified. Results will not be shared with participants, their families, or insurance companies.

4.4.3 Magnetic Resonance Imaging (MRI)

1. All women able to become pregnant will provide a urine sample for a pregnancy test performed no more than 24 hours before MRI. Women who are discovered to be pregnant on their follow-up visit #4 will not participate in the imaging portion of this study.
2. The research coordinator or assistant will escort the participant to the Tesla MR System in the CNRM Neuroimaging Core, housed at the NIH Clinical Center and will monitor the participant throughout the procedure.
3. Subjects will be screened for MRI safety using the Screening Questionnaire used by the Radiology and Imaging Sciences Program of the Clinical Center (Appendix F). Final approval to continue with study MRI procedures will be the responsibility of study investigators.
4. Subjects may be asked to lie still for up to 7 minutes at a time. They will be fitted with earplugs or earmuffs to lessen the loud knocking noise before being placed in the scanner. They can communicate with the MRI staff at all times during their scan, and they may ask to be moved out of the machine at any time.
5. Participants will have a structural MRI scan that does not require contrast. They are not required to do any tasks during the structural MRI. Sequences used for the structural MRI include T1 Magnetization Prepared Rapid Gradient Echo (MPRAGE), Fluid Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI), resting state functional connectivity (rfMRI), diffusion weighted imaging (DWI), Arterial Spin Labeling (ASL) to assess resting CBF, gradient echo (GRE) and/or T2* susceptibility weighted imaging (SWI). If the image quality of a given sequence is inadequate due to patient motion for example, these may be repeated at the discretion of the MRI technologist or radiologist. The structural scan takes approximately 45 minutes.
6. Subjects will also have a scan to measure resting functional connectivity at diagnostic visit and at follow up visit after 1 month of treatment with methylphenidate. Recent studies conducted by Dr. Volkow in cocaine addiction participants showed that short-term methylphenidate administration within 2 hours reduced an abnormally strong connectivity of the ventral striatum with the dorsal striatum (putamen/ globus pallidus), suggesting that methylphenidate can remodel abnormal circuitry [24]. Therefore, one month will be a sufficient interval between two fMRI scans to study functional connectivity after methylphenidate administration.
For this purpose an fMRI scan is obtained while subjects rest with their eyes open in the scanner without any stimulation. An echo-planar imaging (EPI) time series (TE/TR: 20/1600 ms, 200 kHz bandwidth, 64 × 64 matrix size, 20 × 20-cm^2 field-of-view, 35 coronal slices, 4-mm thickness, 1-mm gap, 187 time points, scan time) will be acquired. RFC will take approximately 15 minutes to obtain.

4.4.4 Neuropsychological Assessments

Clinical phenotyping is critical for studying the effect of TBI on memory, behavior and functioning, because clinical representation of consequences after TBI can vary significantly [25]. All testing will be performed by Clinical Center NIH staff. Testing will be administered by a neuropsychologist or psychometrist. We anticipate that the core phenotyping assessments will require approximately 1 hour to complete. These assessments will be done on diagnostic visit #2 and follow up visit # 4. Baseline assessment can be done on visit #1.

Subjects will be given frequent rest breaks. The subject may refuse to answer any question or to stop a test at any time and for any reason.

TBI phenotyping instruments recommended for evaluation in all TBI cohort or natural history studies have been labeled the TBI Common Data Elements (CDEs). The subject will be interviewed, complete questionnaires, take pen-and-paper tests, and perform simple actions.

In this study, we will include the following selected subset of assessments taken from the CDE's:

1. Glasgow Outcome Scale-Extended (GOS-E): is an assessment of the general functioning. This scale evaluates 8 categories: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery (10 min).
2. Learning trials portion of the California Verbal Learning Test (CVLT-II): measures long and short delay free and cued recall, the effects of interference, recognition, and efficiency of learning (5 min).
3. The Trail Making Tests A and B (TMT): visual conceptual and visual motor tracking motor speed and attention The test requires visual scanning, numeric sequencing and visual motor speed (5 min).
4. Subsets of the Wechsler Adult Intelligence Scale (WAIS-IV) (Digit Symbol and Symbol Search): perceptual organization and processing speed (10 min).
5. Brief Symptom Inventory 18 (BSI-18) is used to identify self-reported clinically relevant psychological symptoms in adolescents and adults. The shortened form of the BSI instrument provides a highly sensitive assessment of psychological factors (10 min).
6. Satisfaction with Life Scale (SWLS): is a short 5-item instrument designed to measure global cognitive judgments of satisfaction with one's life (1 min).
7. Word Reading subtest of Wide Range Achievement Test (WRAT)-4: measures the basic academic skills of reading, spelling, and math computation (15 min).

8. Rivermead Post-Concussion Symptom Questionnaire: rate the severity of 16 different symptoms commonly found after a TBI (5 min).

The attention tasks chosen according to Whyte (6) will be administered twice (approximately 60 min).
A neuropsychometrist or neuropsychologist will administer these tests to participants in a private room. Some of the tests are pencil/paper tests; others are computer tests; and some will be verbal question and answer tests. The participant may take breaks. These assessments will be performed twice.

The tests used for measurement of various aspects of attention are shown below:

1. Continuous Performance Test

The Conners Continuous Performance Test 3rd Edition™ (Conners CPT 3™) is a task-oriented computerized assessment of attention-related problems in individuals aged 8 years and older. By indexing the respondent's performance in areas of inattentiveness, impulsivity, sustained attention, and vigilance, the Conners CPT 3 can be useful to the process of diagnosing Attention-Deficit/Hyperactive Disorder (ADHD) and other neurological conditions related to attention.
Administration time: 14 minutes.

2. Auditory Attention

SeaShore Rhythm Test (HRNB). This is a test which requires the subject to attend to two rhythms which are played one after the other and determine if they are the same or different. This test assesses auditory attention.
Administration time: 10 minutes.

3. NIH Tool Box test descriptions from manual Attention

Flanker Inhibitory Control and Attention Test
The Flanker task measures both a participant's attention and inhibitory control. The test requires the participant to focus on a given stimulus while inhibiting attention to stimuli (fish for ages 3-7 or arrows for ages 8-85) flanking it. Sometimes the middle stimulus is pointing in the same direction as the "flankers" (congruent) and sometimes in the opposite direction (incongruent). Scoring is based on a combination of accuracy and reaction time, and the test takes approximately 3 minutes to administer. This test is recommended for ages 3-85.
Administration time: 4 minutes.

The NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory functions, meeting the need for a standard set of measures that can be used as a common currency across diverse study designs and settings. In a short period of time the NIH Toolbox has become the standard psychometric tool in the TBI field, and is being used in two large recently launched multicenter studies (Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) and Chronic Effects of Neurotrauma Consortium (CENC)). It has been adapted in academic medical centers, VA, and Military Treatment Facilities.

The NIH Toolbox was developed by NINDS in cooperation with Northwestern University Research Data Center and is administered through the Assessment Center web

site (http://assessmentcenter.net). Investigators set up a password-protected account with the Assessment Center, which is specific for each study. Access to the study-specific website is only available to study personnel who are provided with a username and password by the Principal Investigator (PI). Testing is carried out through the website. Participant files can include only a study number, age, and gender. We will upload no protected health information to the Assessment Center website. The software program administers the test and provides the scores, which are further normalized for age and gender.

The assessment instruments reside on Northwestern University's server and are only accessible through the secure Assessment Center website. Assessments which have been administered remain on the Northwestern server and are available for use by study personnel who are given access by the PI. The Assessment Center staff does not look at the data for quality control purposes or any other purposes.

For this study, we will use the NIH Toolbox tests (Flanker Inhibitory Control and Attention Test and the Pattern Comparison Processing Speed Test) as it has become the standard in the field, and particularly appropriate for measuring Processing Speed, using computerized assessment tools. No PHI will be entered into the Assessment Center website.

4. Processing speed

Pattern Comparison Processing Speed Test
This test measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not. Participants' raw score is the number of items correct in a 90-second period. The items are designed to be simple to most purely measure processing speed. The test overall takes approximately 3 minutes to administer. This test is recommended for ages 7-85.
Administration time: 4 minutes.

Total Administration time for the attention battery is 32 minutes.

The tests to be used to identify processing speed are the WAIS-IV Processing Speed Index (PSI) and the NIH Tool Box, Processing Speed (Pattern Comparison Processing Speed Test). The PSI is a TBI CDE and Pattern comparison is an NIH Tool Box component. Both of these tests yield demographically adjusted standard scores with a mean of 100 and standard deviation of 15.

A unified score can be the average of the two scores either as an average standard score or after conversion to a deficit score. The retention of the standard score allows for a maintenance of a wider score range and likely easier statistical analysis.

The tests used to identify attention will be the Conners Continuous Performance Test 3rd Ed.(CPT 3), the SeaShore Rhythm Test (SSRT) from the HRNB and the Flanker Inhibitory Control and Attention Test from the NIH tool box. The results from the CPT 3

and the SSRT are reported as demographically adjusted T-scores (mean of 50 and SD or 10). While the NIH tool box reports scores in standard score format (mean of 100 and SD of 15). In addition the CPT 3 provides measures of multiple aspects of attention. Attention being more complex a construct than processing speed it is recommended that the various scores are all used independently to examine if the treatment differentially affects various aspects of attention. Thus a unified score is not recommended for this cognitive domain.

4.4.5. TMS (measurement of intracortical inhibition)

The TMS procedure will be performed before and 60 minutes after methylphenidate (60 mg by mouth) administration. EMG electrodes will be applied to the optimum position for recording the MEP response from the abductor pollicis brevis or first dorsal interosseous muscle. TMS will be delivered through a round coil at the optimal position for producing an MEP in the target muscle. Resting and active motor threshold (RMT and AMT) will be measured after oral methylphenidate. Then, short-interval cortical inhibition (SICI) will be measured with a conditioning pulse just before the test pulse. Twenty trials at each interval and 20 unconditioned test pulses will be delivered in random order.

TMS without and with oral methylphenidate will be performed on Visit #2. Tests with placebo or methylphenidate can be also administered separately at visits #1 #2 or #3. TMS with placebo and with methylphenidate requires 2 hours 40 min in total.

4.4.6. Effort and reward task (motivation test)

This experimental task measures the subject's preference for making hard and easy efforts (muscle contractions) under differentially rewarded conditions. We consider the willingness to perform a given effort for a given reward values a measure of motivation and rewardability.

In this task, visual feedback showing the degree of muscle activation is given to subjects as they make a contraction with the left hand; the EMG is recorded continuously with surface electrodes. During each trial, two targets appear on a feedback display, corresponding to 20% and 60% of the individual's maximum voluntary contraction. Each target is randomly assigned a monetary reward value: One target is labeled '$0.75' and the other is labeled with a value ranging from $0.75 to $1.25, chosen from a random distribution of $\$0.75 - x$ with mean of $x = 0$ (i.e., the mean difference between the target values is $0 across trials). Subjects are asked to choose which monetary value they would like to earn by making a contraction to bring the feedback bar to the corresponding target. Rewards are given intermittently, such that in half the trials (randomly assigned), the subject receives the chosen value and for the other half, they receive no money.

For each trial, the stimulus screen and the subject has up to 10 s to make one of the two muscle contractions. The contraction must be held for 1.5s for the response to be

registered. As soon as a response is entered, the stimulus disappears. The next screen either reads, "You won $X.xx [the chosen value]" or "Sorry, no prize". Finally, after 2s, a fixation cross appears for 6s.

In previous experiments in healthy subjects, we found a consistent preference for the lower effort and that the effort intensity choice is a function of the difference in reward values associated with the 20% and 60% contractions. The probability of choosing the high effort at a given difference in reward values approximates a logistic function, which we would expect to shift to the left (higher likelihood of choosing high effort for a given difference in reward) when motivation and rewardability are higher. This study will be performed on Visit #2. Experiments can be performed on separate days. Part of the test can be also administered on visits #1 or #3 and requires 40 min.

4.4.7 Study Medication

Participants will take methylphenidate (Ritalin), which is FDA-approved and used most often in children to treat attention deficit hyperactivity disorder (ADHD). Methylphenidate is a drug acting on DA neurotransmission commonly used off label by physiatrists attempting to improve recovery after TBI. It acts by directly stimulating release of DA and NE, as well as blocking catecholamine reuptake. In this study, the drug will be taken in a therapeutic dose which significantly increased extracellular DA in the brain [11]. Duration of treatment is chosen based on a prior randomized controlled trial of oral methylphenidate in patients with chronic deficits after TBI, which demonstrated increased processing speed after 3 weeks of oral administration of methylphenidate [6]. The dosage of methylphenidate 60 mg/day was given to moderate to severe TBI patients in this study. In this study the participants received methylphenidate in double blind, placebo-controlled study in dosage 0.3 mg/kg twice a day, with a range 15-40 mg twice a day (30 mg twice a day mg per day per 100 kg body weight) for 6 weeks. From total 39 participants consented for the study, only one subject receiving methylphenidate withdrew (due to possible exacerbation of baseline hypertension). This study provides evidence that dosage of 60 mg/ day is safe in TBI participants.

The participants will receive oral methylphenidate 60 mg before the second TMS study during Visit #2. The participants will receive oral methylphenidate 60 mg before the second PET scan during Visit #3. This single dose is chosen based on evidence of increased intracellular DA after oral dose of methylphenidate [11]. Single dose of 60 mg methylphenidate will be used for PET and TMS studies to block dopamine transporters. Justification of use of single dose 60 mg for PET comes from two studies of Dr. Volkow. In the first study the researchers used PET with [11C]raclopride (D2 receptor ligand that competes with endogenous DA for binding to the receptor) to evaluate if oral 60 mg methylphenidate changes extracellular DA in 11 healthy controls. The study showed that oral 60 mg methylphenidate significantly increased extracellular DA in brain, as evidenced by a significant reduction in Bmax/Kd (measure of D2 receptor availability) in striatum (20 ±12%; $p < 0.0005$). These results provide evidence that oral methylphenidate at dose 60 mg significantly increases extracellular DA in human brain. No adverse events were reported (The Journal of Neuroscience, 2001, Vol. 21 RC121). Another study by

Dr. Volkow group showed that oral methylphenidate produced dose dependent blockage of dopamine transporter (measured by PET with 11 cocaine) and the dose 60 mg per os produced the highest, up to 74 % blockage of dopamine transporters. No adverse events after 60 mg administration of methylphenidate were reported on healthy volunteers (Am J Psychiatry 1998; 155:1325–1331). The purpose of this part the study is to measure tonic DA release, which will be evaluated by measuring of binding potential of raclopride (relative to non-displaceable reference region after placebo and methylphenidate administration). In order to be able to show the difference with placebo administration, the highest dosage which shown to be safe and effective (60 mg) in the cited studies will be used in our study.

The participants will receive the study medication during Visit #3.
The maximal dose of methylphenidate in this study will be 30 mg orally twice daily, the dosage was chosen according to Whyte et al. [6]. "Dose titration will be incremental within 6 days (dose-escalation phase), starting at 5 mg orally twice daily for 2 days, and 10 mg twice daily for the next 2 days and then 20 mg twice daily for next 2 days". Then the dose will be increased to 30 mg twice daily starting from day 7 (Table 3).

Table 3. Dose escalation and time on methylphenidate

Phases of methylphenidate administration	**Days of methylphenidate administration**	**Dosage**
Dose-escalation phase	1-2	5 mg twice a day
	3-4	10 mg twice a day
	5-6	20 mg twice a day
Stable phase	7- 28	30 mg twice a day

During dose-escalation phase the participants will have a telephone follow-up to evaluate adverse events (Table 4). Adverse events of methylphenidate which lead to discontinuation are presented on **Table 4A**. Adverse events of methylphenidate which lead to dose pausing and restarting of the drug are presented (but not limited to) on **Table 4B.**

Table 4. Adverse events and action plan for dose-escalation phase of methylphenidate administration.

A	1. Hypersensitivity (skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura) 2. Angina; cardiac arrhythmia; abdominal pain 3. Dyskinesia, Tourette's syndrome 4. Toxic psychosis 5. Abnormal liver function (transaminase elevation) 6. Cerebral arteritis and/or occlusion 7. Leukopenia and/or anemia 8. Transient depressed mood, aggressive behavior 9. Scalp hair loss	Discontinue the drug
B	1. Nervousness and insomnia 2. Anorexia; nausea 3. Dizziness; palpitations 4. Headache, drowsiness 5. Blood pressure and pulse changes, both up and down 6. Tachycardia	Reduce dosage by half. Omit the drug in the afternoon or evening. Follow up for 3 days. 1. If symptoms disappear, return to the previous dosage. Continue on this dosage through the study. 2. If symptoms persist, decrease the dosage by half • Follow up for 3 days. Continue on the reduced dosage, if symptoms resolve. • Discontinue the drug, if symptoms persist at the minimal dose 5 mg/day.

If participants do not experience adverse events, they will continue with this dose for the remaining 3 weeks of the study (stable phase). The participants will have two telephone follow ups during stable dosing.

The target duration of intake of the medication in the stable phase is 3 weeks. In this study all visits can be scheduled within 2 weeks from the target date. In order to provide sufficient medication for 3 weeks' treatment and 2 additional weeks for scheduling, the

patients will receive study medication for 5 weeks. The remaining pills will be returned and will be counted on Visit #4 to evaluate compliance. The leftover drug will be destroyed through NIH CC pharmacy once a research participant completed all procedures, returned unused drugs, and all the data is recorded.

4.4.8 PET Scanning and processing

Scans will be performed with the High Resolution Research Tomograph (HRRT) which has a transverse resolution of about 2.5 mm. An intravenous line will be inserted for administration of the ligand. A swimming cap with small light reflectors will be put on the subject's head. It is used to monitor head position and movement during the scan; the information is used in the PET image reconstruction process to reduce any blurring of the PET images. Subjects will be positioned in the scanner with the brain in the field of view. Prior to the [^{11}C]raclopride administration, a transmission scan will be obtained with a rotating ^{137}Cs source for attenuation correction. Subsequently, approximately 20 mCi of the [^{11}C]raclopride will be injected through an intravenous catheter in an arm vein over about 1 min using a Harvard ® pump and a 90-min dynamic scan will be obtained.

The PET imaging data from the placebo day will be used as a measure of baseline raclopride binding potential, calculated using the Simplified Reference Tissue Model. PET measurements taken following methylphenidate administration will be compared to those derived after placebo administration. This will permit measurement of the reduction in specific binding of raclopride due to competition with DA endogenously released by the methylphenidate challenge (10). The percent change from baseline was proportional to the magnitude of DA release.

Oral methylphenidate in a 60-mg dose or a placebo will be administered and the scan will be done 60 min later, according to the schedule used by Volkow et al. (11). The oral placebo will be administered before the first PET scan and the methylphenidate will be administered before the second one. The subjects will be blind as to whether placebo or oral methylphenidate is administered. They will have about a 2-hr break between the PET scans, or PET scans can be performed on separate days. The participants will have two 90-min PET scans with [^{11}C]-raclopride, a D2/D3 receptor ligand [11].

Total PET scan time will be 4 hrs, and break time will be at least 2 hrs. PET will be done on visit #3. PET with placebo and with methylphenidate can be done on separate days, on visit #1 or visit #2. The radionuclide (C11) half-life is 20 min, and it is rapidly cleared from plasma and whole blood with biliary elimination The first scan lasts for 90 minutes, then the second scan will be done 60 min after administration of dose of methylphenidate, which makes time from the first injection of raclopride to second injection 150 min, which time less than 0.75% of the 1st raclopride dose will be left.

Regions of interest (ROIs) are obtained directly from coregistered [^{11}C]-raclopride scans and structural MRIs as described previously.(1) ROIs are identified for the caudate, putamen, ventral striatum (VS), and prefrontal cortex (PFC) using multiple planes.

D2/D3 receptor availability was measured as the binding potential relative to a nondisplaceable reference (BP_{ND}), the ratio of the distribution volume in each ROI to that in cerebellum minus 1. The difference in BP_{ND} (ΔBP_{ND}) between MP and placebo was used as the measure of DA release.

Findings from the ROI analysis will be confirmed and extended using Voxel-Based Analysis and Statistical Parametric Mapping (SPM).(1) SPM will also be used in exploratory analysis to assess the effect of MP on DA release in extrastriatal brain regions. SPM analysis will be performed on BP_{ND} images (obtained by computing the BP_{ND} for each pixel). A spatial normalization template matching the average BP_{ND} image contrast in the brain was developed using the BP_{ND} images from 20 healthy age-matched controls who participated in prior [^{11}C]-raclopride studies done by Drs. Volkow and Herscovitch using the same instrument and scanning sequence. A 12-parameter affine transformation with 16 nonlinear iterations will be used to register the images to the MNI template provided with the SPM package.

4.4.9 Summary of the study procedures

Missed visits will be rescheduled within 2 weeks of the target date whenever possible. Study physicians may ask the patient to come in for an examination between visits if the patient has persistent side effects. Investigators may refer the patients to their personal physicians to treat adverse side effects or for negative symptoms relating to the TBI.

4.4.9.1 Diagnostic Visit #1:

During Visit #1, participants will see a study physician for examination and medical history. (30 min), will have blood collected (15 min), and urine samples will be taken from women able to become pregnant. Participants will have structural MRI (45 min), and Resting Functional Connectivity (15 min). Visit #1 requires approximately 2 hr 50 min in total.

4.4.9.2 Diagnostic Visit #2:

During Visit #2, urine pregnancy test will be repeated on the same day for women able to become pregnant. Participants have neuropsychological tests (60 min), attention tests (60 min) and TMS with motivation tasks without and with methylphenidate challenge (2 hr 40 min), adverse events will be monitored (15 min).

Visit # 2 can be performed within two weeks of Visit #1. Neuropsychological tests (60 min) and attention tests (60 min) can be performed during Visit #1.Visit #2 requires approximately 5 hours in total.

4.4.9.3Diagnostic Visit # 3:

At Visit #3, women able to become pregnant will have urine pregnancy test, [11C]-raclopride PET scans after placebo and after oral methylphenidate will be performed (4 hr). The study drug will be dispensed to participants (5 min) and adverse events will be monitored (15 min). Visit #3 requires approximately 4 hr 25 min of research time in total.

4.4.9.4 Telephone follow-ups:

All participants will be contacted by a research assistant or study coordinator by telephone to inquire about possible adverse symptoms after methylphenidate administration.

1. The participants will have a telephone follow-up to evaluate adverse events during dose-escalation part of interventional phase of the study (1-6 days after initiation of methylphenidate administration).
2. The first telephone follow up at the stable part of interventional phase of the study will be done 7-14 days after initiation of the drug administration.
3. The second follow-up at stable part will be done 15-28 days after initiation of the drug administration.

The research staff member will review a checklist of the most common side effects. If the participant reports any bothersome side effects, the research assistant or coordinator will inform one of the physician investigators who will follow-up by telephone or in-person with the participant. Instructions for following medication intake will be given, as described in 4.4.7.

4.4.9.5 Follow-up visit # 4:

At Visit #4, participants will see a study physician (15 min), have about 5 teaspoons of blood collected (15 min), have neuropsychological testing (2 hr). Women able to become pregnant will have urine pregnancy test. Participants will have an MRI scan for resting functional connectivity (15 min) and will be monitored for adverse effects (15 min). The MRI and neuropsychological testing tests will be done while patients are under the effects of their medication (methylphenidate taken 1-3 hr before). Patients will return unused study medication (20 min).

Total time for research procedures during Visit #4 is approximately 3 hr 10 min. The time will vary depending on how long it takes the patient to complete the neurocognitive testing if schedules are not running on time.

4.5. End of Participation

Participation will end upon completion of Visit #4, unless there is an adverse event that needs to be resolved. Participants remain under the care of their own health care providers during study participation and after the end of participation.

4.5.1 Communication of Incidental Findings

MRI: A radiologist will officially read all MRI exams. Professional fees associated with research MRIs will be paid for by the CNRM project and will not be billed to subjects or the subjects' insurance. All imaging data that are germane to clinical interpretation will be interpreted by a credentialed neuroradiologist. Clinically relevant findings will be reviewed by the medically responsible investigators and, in the context of the entire medical assessment, appropriate treatment and or follow-up will be recommended to the participant as indicated. Unexpected findings on brain imaging that require clinical intervention may occur. Therefore, any research findings on brain images, laboratory or other evaluation that may require further evaluation or impact the subject's medical care will be shared with subjects and their health care providers by a physician investigator. However, this study does not provide treatment and does not replace any therapy that a subject may be receiving as part of standard medical care for TBI.

The study physician/investigator may share some of the results from the MRI and general feedback from the neuropsychological testing on the patient's strengths and areas of difficulty. There are no psychiatric tests in this battery. There is one checklist for depression. If any question about suicidal ideation is answered in the affirmative, the study physician will talk with the patient and call in the CNRM psychiatrist, Dr. Dsurney or an NIH staff psychiatrist if there is a concern about the patient's stability and safety. NIH policy will be followed concerning a patient who may be a danger to himself.

Blood: Blood samples are used for research purposes only.

5. Storage of Data and Samples

5.1 Disposition of Samples at the end of the study

Some of the blood sample from each subject will be analyzed in Dr. Diaz-Arrastia's, (Adjunct PI) laboratory at CNRM. Any samples not immediately analyzed by the co-investigator, Dr. Diaz-Arrastia, will be stored in the CNRM Biorepository. Biospecimens and data provided to the CNRM Repository, which is operated under USUHS Protocol No. CNRM-004 "Biorepository and Informatics Warehousing", with Dr. Brian M. Cox as PI, will be coded using a Global Unique Identifier (GUID). Access to specimens maintained by CNRM at the Biorepository is under the supervision of Dr. Cox. An MTA is under negotiation between NINDS and DOD regarding the blood samples and data collected at NIH and stored at the CNRM Biorepository. Biorepository protocol (see Appendix H).

Blood samples will be stored in secured freezers at the CNRM Biorepository. The subject's name and identifying information will not be on the samples; we will assign them a code. The samples will be stored for up to 20 years. The purpose of the repository is to store a large number of samples and related data so that we can learn more about TBI and how to rehabilitate people who may have it. The CNRM is a Federal medical research program of the U.S. Department of Defense (DOD), and DOD is the custodian of the samples. The Uniformed Services University operates the CNRM and the USU IRB reviews the repository for patient protection and receives reports from a Biorepository Steering Committee on the operations of the repository.

Dr. Eric Wassermann is responsible for samples at the NIH and until they are received at the CNRM Biorepository. Before sending blood samples, we will remove the subject's name and identifying information; we will assign them a code. The key to the code will be kept in a separate, secure area. Once the coded samples arrive at the CNRM Biorepository, a repository manager will be responsible for maintaining the samples and sending them to others who may use the samples for research. Subject's blood samples will only be accessible by current and future CNRM investigators after approval by all relevant IRBs.

The investigators may share data including imaging data, with outside investigators or collaborators but only after all identifying information is removed. The subject's data, including imaging data, will be stored t the CNRM Image Processing Core database at NIH. These data may be used for a variety of research purposes including future genetic research that we may not be able to specify at this time.

If a subject wishes to remove his samples, they may contact the principle investigator, Dr. Wassermann, in writing or verbally. If the samples are in the CNRM Biorepository, this person will notify the CNRM of the subject's code and his samples and all associated data, including processed images, will be removed from the repository and related databases and destroyed.

5.1.1 Data identifiers – GUID

The CNRM Informatics Core is ultimately responsible for storing all de-identified data collected under this protocol on behalf of the DoD. Prior to the transfer of the de-identified data from the PI to the CNRM data repository, the PI is responsible for the data. The PI remains responsible for the identified data. The CNRM Informatics Core does not have access to identified data.

The Informatics Core is led by a Principal Investigator, Yang Fann, PhD, who reports directly to the Informatics Core Steering Committee. Data entry into the CNRM Informatics Core database will be limited to the PI of the Informatics Core, Dr. Yang Fann and database administrative staff. The PI of the Informatics Core or a designated database administrator will be responsible for uploading data to the CNRM database.

All data will be coded (de-identified) by removing the 18 specific elements of protected health information (PHI) as defined within the HIPAA Privacy Rule including:

1. Names.
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4. Telephone numbers.
5. Facsimile numbers.
6. Electronic mail addresses.
7. Social security numbers.
8. Medical record numbers.
9. Health plan beneficiary numbers.
10. Account numbers.
11. Certificate/license numbers.
12. Vehicle identifiers and serial numbers, including license plate numbers.
13. Device identifiers and serial numbers.
14. Web universal resource locators (URLs).
15. Internet protocol (IP) address numbers.
16. Biometric identifiers, including fingerprints and voiceprints.
17. Full-face photographic images and any comparable images.
18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Of these 18 elements, the only one that represents a key clinical/scientific value is the date-related fields. In the coded (de-identified) data submissions, age will be reflected as years, as permitted.

In order to de-identify the specimens, the CNRM Informatics Core will establish an encrypted system to generate a globally unique identifier (GUID) from PHI data. The GUIDs approach was originally created for the National Database for Autism Research (NDAR) and the Simons Foundation Autism Research Initiative. The GUID system of the CNRM was established in collaboration with the NDAR staff at the NIH Center for Information Technology, but operates independently of the existing NDAR GUID system, under the support of the CNRM Informatics Core. The GUID is a computer-generated alphanumeric code that is unique to each research participant and, through the use of a one-way hash algorithm, does not allow mapping back to an individual. The

process of assigning a GUID keeps any personally identifying information from ever being transmitted or stored in the CNRM database and prevents such identifying information from appearing with the clinical data.

5.2 Repository for Data

The PI of this protocol will maintain master keys matching GUIDs to samples and data. Electronic master keys will be kept on password protected terminal(s) in locked rooms with limited access. Electronic master key records will be backed up electronically at least weekly. Physical printouts/copies of master keys will be kept in a locked cabinet in fire- and water-proof enclosures with controlled access and will be updated monthly or at more frequent intervals. The mapping from PHI to GUID will not be stored by or known to the CNRM Informatics Core or NIH CIT personnel, but by the central registration of issued GUIDs and the protocol PI with the master keys.

All specimens and data will be stored linked to this GUID. CNRM master keys will contain the following information: GUID, last name, last 4 digits SSN, date of birth, and/or medical record number.

The CNRM Biorepository will maintain a web-based Biorepository Information Management System. The system includes the following types of information: specimens received, specimens processed, method of specimen storage, method of specimen transport, contacts for specimen transport to specific studies, specimens distributed to other CNRM studies, as well as quality control information (acquisition of correct specimen, rapid specimen preservation, timely transportation to the Biorepository, routine and continuous monitoring).

Access to data will only be available to the CNRM Biorepository Manager, PI on this protocol, or designated staff on this protocol. All data and samples under this protocol will be obtained in an identifying manner. Once the specimens and pertinent clinical records or accompanying data are confirmed for quality care purposes, all specimens and data will be de-identified (coded) (maintained/stored remotely) without protected health identifiers. The PI of this protocol will maintain master keys, matching de-identified (coded) samples and data. We will act consistently with the HIPAA regulations. The CNRM Bioinformatics Repository will provide for the imaging and CTDB data to be periodically transferred to NIH CIT, where the data repository is to be housed. All paper records regarding subjects will be kept in folders in locked, secure areas.

5.3 Withdrawal and destruction of data and samples: Participants will be allowed to withdraw from the study at any point. The study investigators may also withdraw participants for medical, administrative or issues of noncompliance. If a participant withdraws voluntarily or is withdrawn from the study, any remaining unused samples and/or data identified as theirs will be destroyed at their request. If they do not request that their samples and data be withdrawn/destroyed, they will continue to be used in the analysis as applicable.

5.4 Repository for Samples

The draft of MTA is in the process of being finalized. The samples belong to CNRM (collaboration between NIH and DOD) and will be stored at the CNRM Biorepository at 12725 Twinbrook Parkway, Rockville, MD, 20852. The draft is attached as Appendix E.

6. Additional Considerations

6.1 Research with Methylphenidate: Investigational New Drug Exemption from FDA. FDA has granted an exemption from IND regulations for this study (see attached letter). The number is (TBD) (Appendix I)

6.1.1 Source of methylphenidate and placebo storage and handling:
The research pharmacists at the NIH research pharmacy will manufacture the methylphenidate (30 mg) so that they are without markings. The storage bottles will have child-proof caps. The NIH research pharmacists will be in charge of storing, randomizing, dispensing to study personnel, and destroying the study medication. The study coordinator, research assistant, or investigator may retrieve the medication from the NIH pharmacy and deliver it to the physician investigator. A licensed physician investigator listed in this protocol as having this privilege will dispense the study medication to subjects.

6.1.2 Package Insert (Appendix B)

6.2 Gene Therapy: There is no gene therapy in this study.

1. Risks/Discomforts

7.1 The known risks and discomforts associated with the study procedures include the following:

7.1.1 Blood Collection

Subjects may experience minor discomfort associated with blood sampling. Minor bruising or infection may occur at the site of needle entry. There is a very small risk of fainting during the procedure. Standard phlebotomy procedures will be used, including seating the patient during the procedure and a short period of observation afterwards.

7.1.2 MRI
Subjects are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery

pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. Volunteers will be screened for these conditions before having an MRI, and if any are present, the MRI scan will not be performed. Volunteers will be asked specifically about metal objects being present in their body. If it is unknown whether metal is present and or if there is any question, MRI will not be performed.

Subjects with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss.

It is not known if MRI is completely safe for a developing fetus. Therefore, all women able to become pregnant will have a pregnancy test performed no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.

Steps taken to minimize risks associated with MRI:
Potential participants will be screened for safety by the Imaging Center tech using the NIH screening checklist prior to each MRI.

During the MRI and PET scans, monitoring equipment (blood pressure, oxygen saturation and/or heart monitoring) will be utilized as medically indicated, and the subject can be observed directly through a window between two rooms or via closed circuit television. In addition, audible communication between the patient and the scanning personnel is possible via intercom. Subjects can be removed from the scanner immediately upon request or in case of medical necessity.
All subjects having a research MRI will be fitted with hearing protection.
Pregnant women are excluded from this study.

7.1.3 Neuropsychological Testing

There are no known risks to participants answering questions about distress, pain, fatigue, depression or anxiety. Possible adverse experiences include mild psychological distress or discomfort by rating one's distress or boredom from answering questions.

Steps taken to minimize risk: Prior to testing, the investigator administering the tests will encourage subjects to try their best, remind them that no one performs perfectly on these tests, and that the tests may be stopped at any time and for any reason. If a participant becomes emotionally distressed while completing any of the instruments, they will be informed that they may postpone or stop the procedure and decline participation altogether.

The psychological measures will be monitored by the investigator after administration for clinically significant symptoms. If a participant discloses information during completion of the assessment form that suggests a danger to themselves or others, or suggests a need for psychiatric intervention, the PI will be notified and will offer referral as appropriate

for psychiatric or other evaluation with a clinician and/or for psychiatric assistance with a provider in their home community together with follow-up by telephone to assure that psychiatric intervention was obtained. Moreover, should the questionnaires in this study raise issues a participant would like to discuss further, the PI will be available to him or her.

7.2 Risks associated with methylphenidate

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening.
Other reactions include: hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy.

There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; aggressive behavior; a few instances of scalp hair loss. There are very rare reports of neuroleptic malignant syndrome (NMS), and, in most of these, patients were concurrently receiving therapies associated with NMS.

Table 5 lists adverse effects reported in a temporal relationship using methylphenidate during the post-marketing experience. Frenette [8] evaluated the safety of methylphenidate used for severe TBI in 14 randomized controlled trials and the following side effects were reported:

Table 5. Evaluation of Safety and Side Effects of MPH in patients with severe TBI (adapted from [8]):

Side effects	***Number of events***	***Studies***	***Comments***
Rash/itching	5	Alban et al., 2004[26].	
Seizures	2	Moein et al., 2006 [27].	
Delirium/ confusion/ hallucinations	4	Alban et al., 2004 [26, 27]	
Hemodynamic changes	?	Lee et al., 2005[28], Alban et al.,2004 [26], Moein et al., 2006[27].	Statistically more prevalent than with placebo ($p < 0.05$) (Moein et al., 2006[27], Alban et al., 2004[26]).
Dizziness/ lightheadedness	2	1 patient withdrawn because of lightheadedness	

		and 1 patient withdrawn because of dizziness (Whyte et al., 2008).	
Diarrhea/ constipation	2	Alban et al., 2004[26].	
Nausea/vomiting	2?	Alban et al., 2004;[26] Lee et al 2005[28].	
Headache	?	Plenger et al., 1996[29].	
Anxiety	7	Plenger et al.,1996 [29] Alban et al., 2004[26].	
Tremors	4	Alban et al.,2004[26].	
Sleep disorder/ drowsiness	12	Alban et al.,2004[26].	Statistically more prevalent than with placebo ($p < 0.05$) (Alban et al., 2004)[26].
Others	4 Irritability; 11 reduction in appetite; 2 difficulty in urinating; 2 blurred vision; 6 dry mouth; 2 weakness; 1 sexual disability	Alban et al., 2004[26], Willmott et al., 2009[30].	Irritability and reduction in appetite statistically more prevalent than with placebo.

Steps taken to minimize risks of methylphenidate:

There will be a telephone follow-up 2 weeks after Visit #2 with all participants. Instructions with methylphenidate dosage will be given, as described in 4.4.7, to participants experiencing adverse events. Telephone follow-up and clinic visits will give physician investigators an opportunity to interface with participants. Participants will be instructed to call 911 or go to the nearest emergency room in the event of a serious symptom that requires immediate medical attention. Investigators will carry a pager and will be available to the study participants for questions or concerns about side effects that are not judged to be emergencies.

Study participants will be cautioned against taking medications that may have possible adverse interactions with methylphenidate. Licensed physician/investigators may prescribe medication for headache or other minor side effects. Otherwise, patients will be instructed to seek medical attention from their personal physician.

Emergency medical problems will be managed by the NIH Rapid Response Team or the Code Blue Team. Participants will be evaluated and can be admitted to 7SWN Neurology Unit, or 3SWS Intensive Care Unit, as needed, under circumstances including, but not limited to:

•Seizure
•Severe psychiatric symptoms, such as anxiety, akathisia, psychosis
•Any other unforeseen complication requiring acute medical stabilization

Care will be provided until the subject is stable, can continue research participation or until care can be transferred to the subject's own health care providers. For medical problems or conditions that occur outside the NIH Clinical Center, participants will need to seek care and treatment from their primary care physician or a local emergency room.

To prevent risks of methylphenidate on the fetus, sexually active women who are able to become pregnant must agree to use an effective method of contraception as stated at 11.6 of the protocol. In addition, women able to become pregnant will have pregnancy tests done before PET, MRI and TMS.

7.3 Risks of review of records

Subjects may be at risk if medical record data are released or viewed by individuals not associated with this research study. IRB-approved investigators will review all subject data only and information obtained for research purposes will be stored in locked offices as described in Section 19, "Confidentiality".

7.4 Risks of sharing research data

Samples and data provided to the CNRM Repository, which is operated under USUHS Protocol No. CNRM-004 "Biorepository and Informatics Warehousing", Dr. Brian M. Cox, PI will be coded using a Global Unique Identifier (GUID) derived from PII and generated locally. Re-identification of data and samples collected at the NIH would be possible if repository data and samples are released with the GUID to other CNRM investigators who have access to the same subjects PII through participation in other IRB approved studies as they will generate the same GUID at their site. Re-identification is unlikely, however, as the CNRM Repository intends in most cases to release data and samples without the GUID.

Steps taken to minimize risks of breach of confidentiality of records or data:
The following measures will be made to minimize foreseeable risks:
• All research procedures will be conducted by staff qualified to perform the procedure and with monitoring as defined in sections 8 and 11.
• Confidentiality will be protected as described in Section 19.
• Use of subject data that is re-identified through PHI used to generate a GUID is permitted only under IRB approved protocols with pre-defined research questions.

7.5 Risk of TMS

There is an extremely small but existent possibility of a seizure during TMS. The danger is even lower with non-repetitive single or paired pulse TMS (<1 Hz), as in this study. Extensive use in our laboratory has not resulted in any difficulties with the device that could pose a hazard to healthy volunteers or patients. TMS can lead to hearing loss in experimental animals by means of the click produced by the stimulating coil when the inducing current is passed through it. However, we found no evidence of chronic hearing loss in several of our normal subjects who were extensively studied with TMS, nor did we find transient changes in several subjects tested before, and immediately after, stimulation. TMS does not appear to pose any hazard to the brain beyond that of electric stimulation, which has been in clinical use for decades. The procedure appears to be safe and without any side effects. Some of the original subjects have been stimulated many thousands of times. The World Health Organization task group and the Food and Drug Administration concluded that brief exposure to static magnetic fields up to 2 Tesla would have no adverse effects on human health. Currently available single pulse or bistim module stimulators do not produce thermal damage to tissues. No significant changes could be documented in cortisol or prolactin levels after TMS. After studying thousands of patients world-wide, only 3 seizures were reported that were possibly related to single-pulse TMS. These occurred in patients with underlying epileptogenic brain lesions. The only known transient side effect is headache, which usually fades over a few hours and responds well to non-steroidal anti-inflammatory drugs.

7.6 Risk of PET

Radiation exposure during the PET scan: This research study involves exposure to radiation from 2 PET scans that use a total of 20 mCi X 2 (40 mCi). of the [^{11}C]raclopride, plus a small amount of radiation from the transmission scan done to calibrate the scanner. The amount of radiation subjects will receive in this study is 1.0 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Risks of intravenous catheterization: Subjects may experience minor discomfort associated with intravenous catheterizations. Minor bruising or infection may occur at the site of needle entry. There is a very small risk of fainting during the procedure. Standard procedures will be used, including seating the patient during the procedure and a short period of observation afterwards. There is no known allergy to raclopride.

8. Subject Safety Monitoring

8.1 Monitor for individual subjects during participation in study procedures

Physicians and study staff in this study will monitor subjects throughout the protocol procedures. Physicians and study coordinator or other research staff member will be with the participant and will monitor for any anxiety and will assess any issues that arise such as suicide ideation. Procedures are done at the NIH Clinical Center and medical emergency services are available to participants in this study, if needed.

The study coordinator or research assistant and MRI technician will be present during all MRI and PET procedures. A study physician will be available by telephone and pager. The study coordinator or research assistant will monitor adverse effects from a single dose of 60 mg methylphenidate administered during either the PET or TMS session.

Additionally, the coordinator or research assistant will contact all participants three times by telephone during four weeks of interventional phase of the study, to inquire about possible adverse effects and review the Symptoms Checklist. Women able to become pregnant will have pregnancy tests at each clinic visit.
Participants remain under the care of their own physicians during participation in this study. Any adverse events reported to their own physicians will be recorded.

8.2 Parameters to be monitored

Physiological side effects (adverse events) of study medication will be monitored in this study. Medication administration compliance will also be monitored.

8.3 Toxicity

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. The patient will be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, a carefully titrated dosage of a short-acting barbiturate will be used before performing gastric lavage. Other measures to detoxify the gut include administration of activated charcoal. Intensive care will be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

8.4 Criteria for Stopping Procedures in an Individual

Participants will be instructed that if they develop adverse effects from the study drug (either methylphenidate or placebo) they are to call the study coordinator to report and document the adverse effects. If the participants will have specific adverse events listed in **Table 6**, the actions will be taken according to the plan below.

Table 6. Adverse events and criteria for stopping methylphenidate and for reducing the dosage (stable phase)

Adverse events	**Action plan**
Nervousness and insomnia	Reduce dosage by half. If symptoms resolve, restart the drug in the minimal dose which did not result in adverse events during the escalation phase. If the symptom persists, discontinue the drug.
Weight loss	Reduce dosage by half If symptoms resolve, restart the drug in the minimal dose which did not result in adverse events during the escalation phase. If the symptom persists, discontinue the drug.
Anorexia; nausea; dizziness; palpitations; headache, drowsiness	Reduce dosage by half. If the symptom persists, discontinue the drug
Blood pressure and pulse changes, both up and down, defined as: 1) Increase or decrease of systolic or diastolic blood pressure registered on 3 measurements on two separate days by 10 mm Hg 2) or increase of BP over 140/90 mm Hg or decrease below 80/60 mm Hg on 3 measurements on 2 separate days Tachycardia defined as increase of heart rate to 100 or more beats per minute when a person is at rest Bradycardia defined as decrease of resting heart rate below 50 beats per minute	Reduce dosage by half. If the symptom persists, discontinue the drug
Hypersensitivity (skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura)	Discontinue the drug
Angina; cardiac arrhythmia; abdominal pain	Discontinue the drug
Dyskinesia, Tourette's syndrome, toxic psychosis	Discontinue the drug
Abnormal liver function (transaminase elevation) defined as increase of ALT > 3 X	Discontinue the drug

upper limit of normal (> 123 U/L for NIH CC)	
Cerebral arteritis and/or occlusion	Discontinue the drug
Leukopenia and/or anemia	Discontinue the drug
Transient depressed mood, aggressive behavior	Discontinue the drug
Scalp hair loss	Discontinue the drug

If study participants will have other adverse effects, which in the opinion of the participant, the investigator, or the participant's physician are sufficiently bothersome to lead to discontinuation, the participant will be asked to discontinue the study drug for 3 days. If the adverse event resolves within three days and there is ambiguity about the causal relationship and the adverse event and the study drug and the adverse event is minor in the judgment of study physician then we may attempt to restart therapy. If the adverse effect disappears with discontinuation of the drug and reappears upon its reintroduction, it will be determined that it is definitely related to the study medication. Participants will then be asked to discontinue the medication, but to remain in the study and return for all scheduled study visits. Data analysis will be carried out under intention-to-treat principles. If it is discovered that a woman is pregnant who has been taking study medication, we will stop medication. She will be followed for the remainder of the study and will be referred to her physician for further follow-up. This will be reported to the IRBs of record.

8.5 Subject Withdrawal

Participants may withdraw from this study for any reason and at any time without penalty. Participants who elect to withdraw from all study procedures will be asked to return the unused medications and will be terminated from the study.

Subjects will be allowed to withdraw from participation in the study at any point without adversely affecting their medical management. Subjects may decline some of the procedures and tests and still participate in this research study. The investigators may also withdraw subjects from the study for medical, administrative or issues of non-compliance. If subjects withdraw, any remaining unused samples that can be identified as theirs will be discarded. Subjects will be offered the opportunity to withdraw their data from the study.

9. Outcome measures

Outcome measures will be neuropsychological tests of CDE (1-8) and tests of various aspects of attention [6] (9-12). These tests will be administered twice, at the visit 2 initial and after 4 weeks of methylphenidate therapy.

1. Glasgow Outcome Scale-Extended (GOS-E)
2. Learning trials portion of the California Verbal Learning Test (CVLT-II):
3. The Trail Making Tests A and B (TMT)
4. Subsets of the Wechsler Adult Intelligence Scale (WAIS-IV) (Digit Symbol and Symbol Search)
5. BSI-18
6. Satisfaction with Life Scale (SWLS)
7. Word Reading subtest of Wide Range Achievement Test (WRAT)-4
8. Rivermead Post-Concussion Symptom Questionnaire
9. The Conners Continuous Performance Test
10. Sea Shore Rhythm Test (HRNB)
11. Flanker Inhibitory Control and Attention Test
12. Pattern Comparison Processing Speed Test

10. Statistical Analysis

10.1 Analysis of Data for Primary Objective Primary Hypothesis: Tonic DA release (ΔBPND) will be associated with improvement over 4 weeks (i.e., patients with higher tonic DA release will demonstrate greater improvement in processing speed), independent of baseline DA D2/DR receptor binding. Spearman correlation analysis will be used to evaluate relationship of ΔBPND in the striatum and the processing speed. Regression analysis will be used to analyze relationship of tonic DA release in in additional anatomical structures (caudate, putamen, and PFC ROIs) (left and right sides will be averaged) to the processing speed as a primary outcome measure.

The primary objective is to assess the relationship between tonic DA release and change in processing speed after 4 weeks of treatment with oral methylphenidate. The primary endpoint of the study will be change of processing speed. Change of processing speed will be measured separately by WAIS-IV Processing Speed Index (PSI) and by the Processing Speed (Pattern Comparison Processing Speed Test) and will be used as a composite derived as an average of two scores. NIH tool box tests have not been validated in TBI which justifies use of the composite and individual measures of processing speed. We will use individual and composite scores for assessing processing speed.

The primary outcome is change in information processing speed during neuropsychologic testing.

During data review, it was noted that the PSI was not administered to five subjects because of an error in the list of tests the neuropsychology technicians were using. The Toolbox PS was not administered to one subject. The Conners CPT was not administered to one subject due to a technical problem with the computer used for the test. Six subjects were affected.
Due to this oversight, half of the primary neurocognitive outcomes were not collected on 6 out of the 11 subjects we tested.

We propose to use a subset of the tests which have already been administered to most of the enrolled participants for our outcome analysis. The Conners Continuous Performance (CPT) test and Toolbox Processing Speed were administered to 10 out of 11 currently enrolled subjects.

Conners CPT was recently tested on military veterans with an average age of 35 years and average education of 14 years, which corresponds to the population in our study[31]. The military test results showed good sensitivity of Conners CPT for memory problems and good ability to discriminate individuals with decreased attention[32].
The Toolbox Pattern Comparison Processing Speed Test was successfully tested on 4,859 participants[33]: the study found that it is appropriate for use in the age cohort of participants in our study and the test has good test-retest and discriminant validity.
Therefore, we propose to use the Conners CPT and Toolbox Processing Speed Test as outcome measures for measurements of processing speed and attention in this study. This will allow us to use the data already collected from our patients with confidence that these measures will allow us to reach our outcome goals.

Analysis plan:
1. We plan to analyze outcomes of all (enrolled and planned) participants using Toolbox Pattern Comparison Processing Speed Processing Speed and the Conners CPT.
2. We will continue to collect all outcome measures of processing speed for all future participants when the study is once again open to recruitment.
3. After we complete data collection, we plan to conduct data analysis including the 4 outcome measures of processing speed on the subset of participants who have all data collected.

10.2 Power Analysis for Primary Objective.
The change in processing speed over 4 weeks of methylphenidate therapy will be correlated using Spearman's non-parametric test to ΔBPND, a measure of tonic DA release. We hypothesize that there will be a positive correlation between the change (improvement) in processing speed and both the level of baseline DA receptor binding as well as with tonic DA release, but that the correlation will be stronger with the latter.

With a sample size of 30, power = 0.80, alpha = 0.05, the study is powered to detect a correlation coefficient of 0.45. This is considered a medium correlation, and is lower than the correlation of 0.55 found in the study on ADHD by Dr. Volkow et al [11]. Power calculations done using web-based calculator found at: www.stattools.net/SSizcorr_Pgm.php.

The third and fourth secondary hypotheses are purely exploratory and there are insufficient preliminary data to allow a power calculation.

We initially excluded participants with BMI > 30 because of potential uncertainty about how obesity and overweight might affect dopamine receptor availability for binding raclopride. Then we increased the allowable maximum body mass index (BMI) from 30 to 40 in the exclusion criteria. The study is unlikely to have the statistical power to use BMI as an independent variable.

The initial sample size for the study was calculated based on a similar study conducted by Volkow (Volkow et al., 2001). That study measured the correlation between dopamine release (as measured by 11C-raclopride PET) and improvement in attention tests after methylphenidate treatment and found a significant correlation with R = 0.55. Initially, for the current study we calculated a sample size of 30 using a more conservative correlation of 0.45. Based on this sample size calculation, we received funding from CNRM to enroll 30 patients.

During implementation of the protocol it was noticed that the attention tests which represent the main outcome of the study were inadvertently not collected on 6 of 11 patients, diminishing the number of subjects available for analysis of the main study outcome. This was reported to the IRB as Problem Report III (submitted 07/08/2015).

Furthermore, after one year of the study the charges for PET studies which were significantly more than anticipated. The study is funded by CNRM, and funding was allocated for 30 scans ($4000 each) or $120,000 for the study. In August 2015 the project was billed for the first time at $164,877.07 for 46 PET studies. Our study team was not aware that the PET Department only sends out a single annual bill and charges for all reserved PET time slots, even when a slot is canceled over 2 weeks in advance. While we anticipate receiving additional funding to allow us to complete the study, we feel it is judicious to recalculate the sample size based on the results of the original 11 patients enrolled regarding the correlation between dopamine release and improvement in attention scores.

We intentionally used conservative assumptions to initially calculate the sample size. After consultation with the USUHS statistician, Dr. Cara Olsen, the sample size can be less conservative and if we assume the same correlation as found in the study by Volkow. Using 0.55, 22 patients will be sufficient to test our hypothesis demonstrating a relationship between dopamine release and change in processing speed after methylphenidate treatment.

We additionally elected to do an interim analysis of the data collected to obtain further support use of the 0.55 correlation as a basis for the power calculation. Of 11 participants enrolled in the study, 2 did not complete methylphenidate treatment due to adverse events, and one subject was not administered one of the neurocognitive tests. Data on 8 participants were available for analysis. We measured non-displaceable binding potential (BPND) before and after administration of 60 mg methylphenidate (MP) in the ventral striatum (VS) as the change in BPND after administration of MP (BPND) is used as a measure of dopamine (DA) release. We selected 10 areas in the VS with maximal DA release and correlated DA release in each ROI with improvement of attention measured by the cognitive outcome measure, the Connors CPT. Per consultation with Dr. Dsurney, a CNRM Neuropsychology Director, a variable Detectability can be selected as the representative outcome. We used Fisher's z Test for Pearson Correlation and SAS program for sample size calculation. The Pearson correlation between DA release in 10 ROIs and change in Detectability was determined as r=0.56036 (0.1039) (mean (SD)) and with range (0.8043-0.4646). This is very close to the value reported by Volkow et al. With r=0.56 and alfa=0.05 and power 0.8, 22 patients will be a sufficient sample size for our study.

Therefore, our interim data analysis supports the use of correlation r=0.55 as originally used in the study by Dr. Volkow and that it can be applied to the sample size calculation for the current study.

11. Human Subjects Protection

11.1 Subject selection: Selection equitability: Subject selection will be equitable. Participants will be recruited from Walter Reed National Military Medical Center (WRNMMC), National Institutes of Health Clinical Center (NIH CC), CNRM Phenotyping Core, CNRM Recruitment Core, regional Veterans Affairs (VA) hospitals, and the National Intrepid Center of Excellence (NiCOE). Subject selection will be equitable. This study allows adults up to age 55 because after that age the incidence of age-related cardiovascular disease significantly increases, potentially confounding results. The racial and ethnic distribution will reflect those of the clinical population affected by TBI in the military as well as in civilian populations. No preference or exclusion will be granted according to gender or ethnic/racial background. We anticipate that approximately 90% of the subjects will be male, because recruitment will include military individuals.

11.2 Justification for exclusion of children: Participants younger than 18 are not included because some of the neuropsychometric measures included in the CDE battery used in this study are not normed for children under age 18. There is no sufficient information how methylphenidate may affect development and recovery of children's brain after TBI.

11.3 Justification for the exclusion of vulnerable populations: pregnant women, mentally ill, and cognitively impaired subjects. We are uncertain whether methylphenidate, PET, MRI or TMS are safe for a pregnant woman or a fetus; thus, pregnant women are excluded from this research study cognitively impaired subjects are excluded because they would not be able to consent for themselves, follow instructions, complete the neurocognitive measures, and be responsible for study medication. Potential participants with mental illness sufficiently severe to impair their ability to provide informed consent will be excluded.

11.4 Justification for sensitive procedures: use of placebo
This trial uses placebo crossover design, but only for PET imaging and for TMS. All participants will receive the active drug during the 4-week administration phase.

11.5 Justification for exclusion of non-English speaking subject: Non-English speakers will be excluded because the neuropsychological assessment instruments we are using are not all validated or normed in other languages. Furthermore, many of the tests we are performing would require a native-speaking psychometrist to administer; such an individual is not available.

11.6 Safeguards for Vulnerable Subjects: Given the morbidity common in symptomatic chronic TBI, we anticipate that several medical or psychiatric complications might arise during the course of the study visits. Participants who exhibit psychiatric complications will then undergo a structured interview by a qualified on-site professional and referred for appropriate medical care by their clinical care provider. Other emergent psychiatric evaluation and treatment will be performed under the guidance of the NIMH Psychiatry Consultation Service.
11.7 Justification for exclusion of NIH Employees

We do not anticipate that NIH employees would be eligible for this study because they would be unlikely to fulfill the inclusion criteria of having a TBI with persistent memory and attention problems and significant impairment of social and/or occupational functioning and be employed full time at NIH. Further, the study procedures are time-consuming and are carried out during office hours over a few days' time. This would require NIH employees to take 3 or 4 days of leave to participate and this would further decrease the likelihood of their participation.

Prior to any PET or MRI scan, urine specimens will be collected and pregnancy tests will be performed on women of child bearing potential. Subjects with positive pregnancy tests will not undergo MRI. Contraception is required for women able to become pregnant as stated at 11.6 of the protocol.

Emergency medical problems will be managed by the NIH Rapid Response Team or the Code Blue Team. Participants will be evaluated and can be admitted to 7SWN Neurology Unit, or 3SWS Intensive Care Unit, as needed, under circumstances including, but not limited to:

•Seizure
•Severe psychiatric symptoms, such as anxiety, akathisia, psychosis
•Any other unforeseen complication requiring acute medical stabilization.

Care will be provided until the subject is stable, can continue research participation or until care can be transferred to the subject's own health care providers.
For medical problems or conditions that occur outside of the NIH Clinical Center, participants will need to seek care and treatment from their primary care physician or a local emergency room.

Contraception requirement for females able to become pregnant

Women able to become pregnant will be required to have a pregnancy test at each clinic visit. Sexually active women who are able to become pregnant must agree to use an effective method of contraception (birth control) from the time they enroll in the study until 2 weeks after they have completed taking the study drug, methylphenidate or placebo.
Effective methods of contraception for this study include:
1. hormonal contraception (birth control pills, injected hormones or vaginal ring)
2. intrauterine device
3. barrier methods (condom or diaphragm) combined with spermicide.
4. surgical sterilization (hysterectomy, tubal ligation, or vasectomy in a partner.

It will be explained to them that it is important to know that no method of birth control is totally effective in preventing pregnancy except for surgical sterilization (hysterectomy or tubal ligation for women and vasectomy for men) and total abstinence from sexual relations.

If it is discovered that a woman is pregnant who has been taking study medication, we will stop medication. She will be followed for the remainder of the study and will be referred to her physician for further follow-up. This will be reported to the IRBs of record.

Rationale for BMI>40 exclusion

In the study we initially excluded participants with BMI > 30 because of potential uncertainty about how obesity and overweight might affect dopamine receptor availability for binding raclopride. Our concern came from a study of Volkow et al.[34]1 in obese people with BMI 42-60 (mean 51), compared to subjects with BMI 21-28 (mean 25). They found that dopamine receptor availability was decreased in proportion to BMI in the obese participants.

Now, however, we are finding that BMI in the 30-40 range is quite prevalent in the moderate TBI population we are targeting for recruitment. Weight loss, while desirable, is not possible on the timescale required for participation and this criterion is proving a significant barrier to recruitment. We note the complexity of the study and the fact that most of our subjects are employed and many have family responsibilities, in addition to the burdens imposed by their injuries. While dopamine receptor availability at baseline

or the change with methylphenidate administration could still differ in our study group under a liberalized BMI exclusion threshold, there are no data to suggest this in the literature.

11.7 Qualifications of Investigators

The Principal Investigator (PI) and associate investigators (AIs) have extensive experience as investigators in acute brain injury including traumatic brain injury, stroke, epilepsy, and Alzheimer's disease, including investigational drug trials. Physicians and clinical investigators will obtain informed consent for this protocol. Trained study investigators will perform medical records data collection and assessment scales.

The specific qualifications of individual investigators are as follows:

Principal Investigator: Eric Wassermann, MD, is a neurologist experienced in traumatic brain injury and neuroimaging. He is head of the NINDS Behavioral Neurology Unit. He will manage and oversee the safety issues of the study, perform physical examinations, determine patient eligibility, obtain informed consent, and respond to patients who call with problems resulting from the study medication. Dr. Wassermann will implement TMS for study participants and may participate in all aspects of the study.

Adjunct Principal Investigator: Ramon Diaz-Arrastia, MD, PhD is a neurologist with more than 20 years of experience in clinical practice and research. He has been a PI for several NIH- and industry-sponsored clinical trials. Dr. Diaz-Arrastia will assist Dr. Wassermann in study management, interview and examine patients, determine patient eligibility, collect blood samples, obtain informed consent, participate in all aspects of the study, and respond to patients who call with problems regarding the study medication.

Associate Investigators:

Nora Volkow, MD, is the director of NIDA. Dr. Volkow has extensive experience in using dopamine agonists in various clinical studies and in use of PET. She will participate in designing and implementing PET imaging studies, methylphenidate administration schedule and dosage, and determining biomarker measurements.

Peter Herscovitch, MD, is the director of the PET department. He will oversee all procedures related to PET imaging.

Tanya Bogoslovsky, MD, is a senior staff scientist at CNRM. She will participate in study design, all aspects of protocol preparation and implementation.

John Butman, MD, is the PI of the CNRM Human Image Analysis core, as well as Staff Neuroradiologist at the NIH Clinical Center. He will assist with all aspects of the MRI and other data analysis.

Dzung Pham, PhD, is the director of the Image Processing Core for CNRM. Dr. Pham will assist with all aspects of the MRI and other data analysis.

John Dsurney, PhD, clinical psychologist, is experienced in clinical trials and will oversee implementing the neuropsychological tests to the study participants and will review and comment on the findings.

Yunhua Gong, MD, will process and assay plasma and serum biomarkers. He will also be responsible for the functional and immunological and other laboratory work.

Bao-Xi Qu, MD, will process the blood samples and assay the plasma and serum biomarkers. He will also be responsible for the functional and immunological assays and other laboratory work.

Kimbra Kenney, MD, is a board-certified neurologist, and Assistant Professor of Neurology at USUHS. Dr. Kenney's role in this project will be to assist Dr. Diaz-Arrastia with patient interviews, obtain consent, blood sample collection, and neurological and physical examinations. She will also respond to patients who call with questions or concerns about the study medication.

Carol Moore, MA, CCRC, will screen, schedule, interview, and follow-up with patients. She will complete case report forms, manage the study, report all types of adverse events. Ms. Moore may also process blood samples in the laboratory.

Christian Shenouda, MD, will interview and examine patients, determine patient eligibility, collect blood samples, obtain informed consent, participate in all aspects of the study, and respond to patients who call with problems regarding the study medication.

Franck Amyot, PhD, is a Research Fellow with the CNRM under Dr. Diaz-Arrastia. His responsibility will be to analyze MRI data and write papers.

Michael Tierney, MA, NINDS (National Institute of Neurological Disorders and Stroke), will perform TMS studies and does not obtain informed consent.

Philip Koshy, BA, NINDS (National Institute of Neurological Disorders and Stroke), will perform TMS, he does not obtain informed consent.

Lisa Christine Turtzo, MD, PhD. Dr. Turtzo is a board-certified neurologist, and Adjunct Assistant Professor of Neurology at USUHS. Dr. Turtzo's role in this project will be to assist Dr. Diaz-Arrastia with the patient interviews, obtain consent, blood sample collection, and neurological and physical examinations. She will also respond to patients who call with questions or concerns about the study medication.

Kris M. Knutson, PhD, NINDS, will analyze MRI and PET data. She will not obtain informed consent.

Erica Silverman, BS, CNRM will screen, schedule, interview, and follow-up with patients. She will complete case report forms, report AE's and SAE's. She will not obtain informed consent.

Listed below are those individuals allowed to obtain consent:

Eric Wassermann, MD
Ramon Diaz-Arrastia, MD
Kimbra Kenney, MD
Christian Shenouda, MD
Lisa Christine Turtzo, MD, PhD.

12 Anticipated Benefits

12.1 Direct Benefit
This study does not offer direct benefit to participants.

12.2 Indirect Benefit
The information we gain from this study may help us more effectively diagnose and treat subjects with TBI in the future. Participants may indirectly benefit from administration of methylphenidate, and that information may be of value in seeking medical care from their primary care physicians.

13. Classification of Risk

This protocol is classified as a more than minimal risk study due to the use of methylphenidate and administration of [11C]-raclopride before PET. Risk is reasonable in relation to anticipated benefit.

14. Consent Documents and Process

14.1 Designation of those obtaining consent: Study investigators designated as able to obtain consent in section 11.6 above, will obtain informed consent.
14.2 Consent procedures: Informed consent will be obtained directly from the participant (no surrogate). At the diagnostic visit, the investigator able to obtain consent listed in section 11.6 above, will explain study procedures, respond to any questions, and obtain consent by obtaining the participants signature on the consent document. A copy of the consent form will be given to the subject, and the consent process will be documented in the subject's chart. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of

their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing.

14.3 Consent documents: The standard consent form contains all required elements.

15. Data and Safety Monitoring

15. 1 Data and Safety Monitor

Data and safety will be monitored by the PI and an independent Medical Monitor.
Dr. William Theodore, an NIH neurologist acting as the independent Medical Monitor, will supervise patient safety.

15.2 Data and Safety Monitoring Plan

The independent Medical Monitor will monitor data and safety in an ongoing manner. The Medical Monitor will be contacted immediately after every serious adverse event (SAE) that is related to the protocol and all deaths and at least quarterly for other SAEs in compliance with NIH and IRB requirements. The study team will provide the Medical Monitor with a report every six months so that he can check for any safety issues and threatening trends. He will provide yearly reports.

As the principal investigator, Dr. Wassermann will be contacted after every SAE that is related to the protocol and notified of all deaths. The Medical Monitor, Dr. Theodore, will also be notified of SAEs by telephone and email. He will provide yearly reports that will be submitted to the NIH and USUHS IRBs with the continuing review. He will promptly report discrepancies or problems to the IRB and shall have the authority to stop the study, remove individual subjects from the study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the independent medical monitor's report.

15.3 Criteria for stopping the study or suspending enrollment or procedures

As Medical Monitor, Dr. Theodore will have the authority to halt the study, remove individual subjects from the study, and take whatever steps are necessary to protect the safety and well-being of research subjects.

The Medical Monitor, PI, and IRBs will assess the measures taken by the study team in response to safety issues that caused the study to be stopped or suspended. Revised safety measures taken by the study team will be in a written report submitted to the Medical Monitor, and IRBs of record. Only when these entities agree in writing that the problems have been satisfactorily addressed can the protocol be re-activated.
There will be an annual continuing review of this study at the NIH and USUHS IRBs.

16. Quality Assurance

This protocol will undergo periodic review by the NINDS Quality Assurance (QA) Audit Committee as outlined in the NINDS QA Standard Operating Procedure. The purpose of the QA audit is to assess compliance with applicable regulatory requirements, good clinical practice guidelines, NINDS policy, as well as to provide recommendations for improving the management of clinical research data. The protocol will be audited according to the decision algorithm as described in the NINDS SOP.

In addition, the NINDS QA team will do extra QA monitoring of the protocol. After the first 3-5 participants are enrolled and every 6 months afterwards, the team will monitor the protocol by reviewing the regulatory documents and to check that the data has been collected in compliance with the protocol and regulations. Any noted deviations and violations will be reported to the PI. The team will issue complete reports of monitoring visits to the PI.

17. Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing on the Problem Report Form not more than 7 days after the PI first learns of the event. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing on the Problem Report Form not more than 14 days after the PI first learns of the event.

Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

The PI will immediately report SAEs to the Sponsor according to the requirements of 21 CFR 312.64(b) and as agreed upon with the sponsor. The PI will record non serious AEs and report them to the Sponsor. There is no requirement from the sponsor to report non serious SAE's within specified time frame.

18. Alternatives to Participation or Alternative Therapies

This study does not replace any therapy that subjects may receive as part of standard care for TBI from their own physician. Subjects may choose not to participate in this study. An alternative may be for his or her own physician to prescribe methylphenidate off label.

19. Confidentiality

Confidentiality of patient files will be maintained at all times. Paper records and case report forms will be maintained in locked rooms, or in computer files protected by computer passwords. The collected data will be accessible only by research personnel. In the presentation of research results, no information will be given that may reveal the identity of the research subjects. The consent form will discuss patient confidentiality protection.

Confidentiality of the patient records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, especially to military personnel, because information bearing on their health may be required to be reported to appropriate medical or command authorities. Representatives of the study sponsor (CNRM), the Henry M Jackson Foundation, US Department of Defense (DoD), and NIH may have access to the study data for audit purposes.

Since we are collecting sensitive information, including data on patient's functional capacity, there is a risk of the release of sensitive information. The risk of breaches of patient confidentiality will be minimized by quickly coding the blood samples and imaging data. In addition, all identified clinical data will be stored in servers that are backed up and password protected, or in locked files in secure areas. Only NIH study investigators will have access to the key to the codes and identifiable data.

Each study participant will be assigned a study number that will be used on study data collection forms and samples. The link between the study number and participants' identity will be kept on a password-protected computer. Only study researchers and members of the IRB will have access to identified information. Data transmitted to the Data Coordinating Center will be coded. Investigators at the clinical site where consent was obtained will have access to identifying information for the patients enrolled in the study at their site. Only coded de-identified information will be shared with persons outside of the enrolling site, except for audits.

NIH will assign a Global Unique Identifier (GUID) to all data submitted to the CNRM Repository. The purpose of the GUID is to allow data on the same subject, from multiple protocols and from different institutions, to be identified as coming from a single individual and to be combined in the repository. PII will be entered on a local server and a one-way encryption using a keyed-hash algorithm will be used to assign the GUID. CNRM will not receive PII. The one-way encryption assures that the GUID cannot be used to back-generate PII. Data that were delinked may then be sent to other non-CNRM Biorepository.

Blood will be processed and frozen according to CNRM Biorepository guidelines for confidentiality. Samples will be assigned a unique identifier at time of blood draw. The key for the re-identification of samples will be maintained on a master list in the PI's office and accessible only to his designees. Some information will be on a password-secured server in one of the Investigator's offices on the NIH campus.
To help us protect the study participant's privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify the participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).
We explained in the consent form that a Certificate of Confidentiality does not prevent the participant or a member of their family from voluntarily releasing information about themselves or their involvement in this research. If an insurer, employer, or other person obtains their written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without consent, information that would identify them as a participant in the research project if they discover child, spousal, or elder abuse or that the participant has an intent to hurt himself or others.

Military: In addition to the voluntary disclosures listed above, participants who are active members of the military will not have guarantees that their information will be kept completely confidential from their Command and their military health care provider. This exception is stated in the Consent Form.

20. Conflict of Interest

NIH guidelines on conflict of interest have been distributed to all investigators. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.
There is no commercial company or sponsor involved in this study.

21. Technology Transfer

A Materials Transfer Agreement (MTA) is being negotiated between NIH/NINDS and DOD. A draft of MTA between DoD and NIH is being prepared and is attached as Appendix E.
The NINDS tech transfer office will require specific information on planned transfer and use of materials or data and documentation of IRB approval for each request from other investigators.

22. Research and Travel Compensation

Study participants will be compensated for their participation in the study. They will receive these amounts for attempting or completing the following procedures:
Blood collection: $20.00, Neuropsychological testing including attention tests: $75.00, MRI: $50.00, each PET $50.00 ($100 for PET with placebo and with methylphenidate). TMS for both placebo and methylphenidate will be $75.
Visit 1 will be compensated $70, Visit 2 $150, Visit 3 $100 and Visit 4 $145. Maximal possible compensation will be $465 for all completed 4 visits. Study participants may also be reimbursed for travel expenses.

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INSTITUTE: National Institute of Neurological Disorders and Stroke

STUDY NUMBER: T-N-2856 PRINCIPAL INVESTIGATOR: Eric Wassermann, MD

STUDY TITLE: Dopamine Receptor Imaging to Predict Response to Stimulant Therapy in Chronic TBI

Initial Review Approved by the IRB on Date Posted to Web:
Standard

We invite you to take part in a research study at the National Institutes of Health (NIH).
First, we want you to know that:

Taking part in NIH research is entirely voluntary.

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

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

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

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

Purpose

You are participating in this protocol because you have suffered a traumatic brain injury (TBI). You may have memory and attention problems . We want to measure the effect of methylphenidate (Ritalin®) on your brain using various brain scans and memory and thinking tests and questionnaires. This will help us to know if methylphenidate is affecting your brain.

Background

Problems in memory, attention, and decision-making are very common after TBI. A brain chemical called dopamine helps with attention and memory. A traumatic brain injury can affect this chemical, dopamine.. Increasing dopamine has been shown to improve attention and memory in some people. Drug called methylphenidate (Ritalin) can increase dopamine levels It is used in people who have problems with attention. We want to see if methylphenidate increases dopamine in a person who had a TBI.
We will use a type of brain scan called positron emission tomography (PET) and another procedure called transcranial magnetic stimulation (TMS). These procedures will show us if methylphenidate is working on your dopamine levels.
We will use a brain scan called magnetic resonance imaging (MRI). It helps us see if you have any injury to your brain.

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.. You will also have memory and thinking tests before and after methylphenidate to see if methylphenidate improves your memory and attention.

Study Population.

We will recruit 30 men and women who had a TBI 6 months ago who are still having problems after their injury.

Inclusion Criteria

You may be eligible for this research study if you:

1. Are 18 – 55 old
2. Had a TBI with any one of the following:
   A. You had a coma score between 3 and 12
   B. You did not remember anything for 24 hours after the accident
   C. You had a brain scan that showed a brain injury

3. Had a TBI and still have problems with memory or attention and at least **one or more** of the following:
   a) unusual tiredness
   b) sleep problems
   c) irritability
   d) you or others notice changes in your personality
   e) you have a hard time getting going, making decisions, or starting activities

These problems or behaviors started after your TBI. Or the problems have gotten much worse if you had some before the accident. These symptoms cause significant problems in the way you now function in your social life or at work. You are not functioning quite as well as you used to before your accident.

4. Can read, speak, and write in English.
5. Can give consent by yourself.

Exclusion Criteria

You may not be eligible for this research study, if you:

1. have penetrating brain injury, like a gunshot
2. cannot take methylphenidate because:
   a. have glaucoma (high eye pressure)
   b. have motor tics or a family history of Tourette's syndrome
   c. have an allergy to methylphenidate (hives, difficulty breathing, swelling of face, lips, tongue, or throat)
   d. anxiety or restlessness which prevents you from doing day to day activities

e. have high blood pressure, heart failure, heart attack, or ventricular arrhythmia (a specific kind of irregular heartbeat).
f. have had psychosis or bipolar illness
g. have had seizures, or known EEG abnormalities in absence of seizures
h. have had spasms in arteries in your arms and legs (Raynaud's phenomenon)
i. have a history of drug dependence or alcoholism (use of drugs or alcohol again despite repeated bad consequences)
j. take Coumadin, a blood thinner, anticonvulsants (such as phenobarbital, phenytoin, primidone) usually used to prevent seizures, and tricyclic drugs (such as imipramine, clomipramine, desipramine) often used for depression, obsessive compulsive disorder, and attention deficit disorder.
k. take monoamine oxidase inhibitors (such as Marplan (isocarboxazid), Nardil (phenelzine), Emsam (selegiline), and Parnate (tranylcypromine)) usually taken for depression and anxiety
l. take blood pressure medication (for high or low blood pressure)
m. are pregnant
n. are breastfeeding

3. Have a disabling neurological or psychiatric disorder not due to your brain injury. Examples of these include multiple sclerosis, stroke (other than stroke at the time of TBI), disabling developmental disorder, epilepsy, major depressive disorder, aggressive behavior, hostility, schizophrenia. A "disabling" neurological or psychiatric disorder is one that prevents you from holding a job or completing your education.

4. Cannot have an MRI, and TMS because you have:

1. metal in or around your eye, such as clip, implants, or other foreign bodies
2. a cardiac pacemaker or auto-defibrillator or pump
3. non-removable body piercing
4. claustrophobia or fear of close spaces
5. inability to lie flat for approximately two hours.

5. You are not able to have TMS if you have a history of seizures.
6. You are already in a drug study.
7. You are able to get pregnant and do not want to use an effective method of contraception during this study.
8. You have a body mass index (BMI) of more than 30. (Waist size multiplied by height is BMI).

Procedures

You will come to the NIH Clinical Center (CC) for four visits during a 2-month period. One of the research staff members will meet and take you to the Neurology Clinic. Visits will last from about 3 to 6 hours.

Consent: One of the study doctors will review the consent form and discuss details of the study with you. You may ask questions and think about whether you want to be in the study. You may also talk about it with your family or friends. If you want to participate in the study, you and the study doctor will sign a consent form. We will give you a copy to keep.

Screening: A nurse will check some of your vital signs such as blood pressure, pulse, and temperature. The study doctor and research assistant will ask you about your health and medical history. They will also ask what medications you take.

We will ask you about your head injury. We may be able to get some of this information from your medical records. If you are a female who is able to become pregnant, we will ask you for a urine sample for a pregnancy test.

If you meet all of the requirements for the study, you will continue with the study procedures.

Procedures after you qualify for the study:

1) Physical and neurological exam: The doctor will listen to your heart and look at your eyes and ears. The doctor will also check your reflexes watch you walk, and do a few other tests. This physical examination is for research purposes only and does not replace any exam your own doctor may do.

2) Blood Drawing: Blood will be drawn through a needle in your arm. We will draw no more than 5 teaspoons (25 ml) of blood at any one time and no more than 11 teaspoons (50 ml) during the entire study.

Study blood tests
We will take blood for genetic studies to see how genes may affect recovery from TBI. No specific genetic tests will be done under this protocol. The blood samples will be stored in CNRM Biorepository and combined with samples from other studies. We will take blood for study of other biomarkers that can tell us about your brain injury. . There will be no screening for illegal drug use.

Future use of samples
testing is one part of the research which may be done on samples submitted to the CNRM Biorepository.
We will not be testing your blood for other clinical purposes.
Please initial one of the following statements regarding your wishes for genetic testing.

_____YES, I give permission for genetic testing on my blood samples.

_____ NO, I do NOT give permission for genetic testing on my blood samples.

_____ YES, I give permission for biological marker testing that relates to TBI

_____ NO, I do NOT give permission for biological marker testing that relates to TBI

Urine sample:, Women who are able to become pregnant will have a urine pregnancy test before participating in this study, before each MRI, PET, and TMS. You will not be able to participate in this study if the pregnancy test is positive. If you become pregnant during the study, you cannot take the drug any more. You also cannot have any more MRIs or PET or TMS. If you become pregnant, you do not have to drop out of the study. We will follow you until the end of the study but we will not give you any more drug or brain scans.

3) Magnetic resonance imaging (MRI): A research assistant will walk with you to the imaging center where you will have your MRI. The MRI technician will ask questions to make sure you can safely have an MRI. You will have an MRI two times during the study. They will happen at Visits 1 and 4. There is no contrast, no shots, or pills to take for the MRI.

MRI uses a strong magnetic field and radio waves to take pictures of your brain. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. You will be in the scanner about 1 hour. We may ask you to lie still for up to 15 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan. You may ask to come out of the scanner at any time. You do not do anything during the MRI.

4) Neuropsychological Testing

Neuropsychological testing may include tests of your memory, attention, concentration and thinking. We may interview you and ask you to complete questionnaires. You may also take pen-and-paper or computerized tests and perform simple actions. This will take about 2 hours. You will have these tests two times during the study, which may be at visits 1, or 2, and 4.

5) Study Drug

DOSING: The study drug will be methylphenidate which you take by mouth. You will take methylphenidate 60 mg or placebo on visit 2 before the TMS sessions.. You will take methylphenidate 60 mg or placebo on visit 3 before PET scans. You will not know when you will be taking the active drug and when you are taking the placebo. In addition, on visit 3, we will give you the study drug for 4 weeks. You will take 5 mg pill two times a day for 3 days and then 10 mg daily for the next 3 days. This is a gradual increase in dose over about a week's time. We will call you one week after visit 3 and will ask if you have had any side effects after taking the drug. If you get: a) allergic reactions, heart attack, stroke, stomach pain, psychosis, get uncontrolled movements in your body, hair loss or mood change, we will ask you to stop the drug. If you get: b) headache, changes in blood pressure or heart rate, or trouble sleeping the doctor will tell you how to lower the dose of the drug. If you do not have any side effects, you will take 30 mg of the drug two times a day. You will take this dose daily until the study is finished. We will call you two more times when you will be on this dose. If you have side effects mentioned earlier as a) from the drug, you will stop the drug. If you get side effects as b), we will ask you to lower the dose. The doctor will tell you how to lower the dose. . You will take this lower dose until the end of the study and not go back up. .. You will take on the day of visit 4. You will return all unused pills. We will count them on visit 4. You will stop taking the drug after visit 4 is completed.

6) TMS

We will do this twice, once before and once after you take the study drug. Each of the 2 sessions is about 80 minutes. For TMS, a wire coil is held on the scalp. A brief electrical current is passed through the coil and creates a magnetic pulse that stimulates the brain. You will hear a click and may feel a pulling sensation on the skin under the coil. There may be a twitch in the muscles of your face, arm or leg. During the stimulation, we may ask you to tense certain muscles slightly or perform other simple actions. We will make some marks on your scalp. The marks will be removed at the end of the session.

At the beginning of each experiment, we will put metal electrodes on one of your hands with tape. We will ask you to relax your arms and hands. We will find the correct stimulation strength needed to activate your hand muscles and then give you about 40 TMS pulses, some of which will actually be pairs of pulses very close together. You can expect to receive about 60 TMS pulses in each session. These will be so close to each other that you will feel just one movement. We will use these measurements of the movements as a baseline for your brain. We will compare them with the movements that are made during the main part of the experiments. TMS with and without the study drug can be done on separate visits (visits #1, #2 or #3).

7) Effort task

You will do this task twice, once before and once after you take the study drug. You will sit in front of a computer screen, which will give you the task instructions. It will ask you to make a movement, which activates a hand muscle a lot or a little. The computer screen will show you how much you are activating it. Sometimes we will give you the choice of how much to activate it. We will pay you different amounts of money to make the different activations. However, you will not be paid every time you activate the muscle. The task takes about 40 minutes. The tasks without and with the study drug can be done on separate visits (visits #1, #2 or #3).

8) PET Procedure

Before performing the PET scan, you will take one dose of methylphenidate 60 mg or placebo by mouth. You will have an intravenous catheter placed in your arm. This is done by using a needle to guide a thin plastic tube (catheter) into your elbow crease area. The needle will be removed, leaving only the catheter in the vein. The catheter will be taped to the skin to hold it in place. The intravenous catheter will be used for the injection of a small amount of the radioactive substance [11C]raclopride. This substance travels to the brain and tells us where a chemical called dopamine is acting.

During the time the catheter is in place, you need to keep your arm still. The catheter should not move. Once the catheter is in place, a swimming cap with small light reflectors will be put on your head. It is used to monitor the position of your head during the scan. You will be scanned for approximately 2 hours after the injection. During the scan you have to lie quietly on the scanner bed. While you are inside the PET scanner, we will be able to hear you speak. After the scan is completed, we will ask you to go to the bathroom to urinate.

Take one dose of methylphenidate 60 mg or placebo by mouth. Take a break for about 1 hour. Have another infusion of raclopride through the catheter in your arm, and repeat the 2-hour PET scan. We will ask you to urinate again after the second PET scan. The scans with placebo and the study drug can be done on the same day or on different days (visits #1, #2 or #3).

The study procedures are described below visit-by-visit. All visits will be done at the NIH Clinical Center.

Visit 1 (will take approximately to 3 hours). During your first visit, you will have the following procedures as described above:
1) Study explanation and sign informed consent
2) Blood draw
3) Urine collection for pregnancy testing (if applicable)
4) TBI history, surveys and medical history
5) Neurological examination
6) MRI

Visit 2 (will take about 5 hours). You will return to the NIH Neurology Clinic within 2 weeks after Visit 1. You will have the following:

1) Urine collection for pregnancy testing, (if applicable)
2) Neuropsychological testing
3) You will have TMS and effort task without and with methylphenidate

Visits 3 (will take about 4.5 hours). You will return to the NIH Neurology Clinic within 2 weeks after Visit 2. You will have the following:

1) Urine collection for pregnancy testing, (if applicable)
2) An intravenous catheter will be placed in your arm to administer the radio dye.
3) You will have PET scan twice once with either placebo or methylphenidate; another time you will take either methylphenidate or placebo. You will not know which one you are taking.
4) We will give you the study drug to take home and give you instructions on how to take it.

Phone calls (will take about 15 min). We will call you three times. The first phone call will be one week after visit 3. The second phone call will be two weeks after visit 3. The last phone call will be 3-4 weeks after visit 3. ou will have the following:

1. We will find out if you have side effects or allergic reactions.
2. We will tell if you need to change your drug dosage.

Visit 4 (will take up to 3 hours). You will return to the NIH Neurology Clinic 4 weeks after visit 3. You will repeat the following:

1) Blood draw
2) Urine collection for pregnancy testing (if applicable)
3) The research assistant will review a list of symptoms with you.
4) You will have an interview with one of the study doctors to discuss any symptoms you may have experienced.
5) Neuropsychological testing
6) MRI
7) You will return unused pills.

Risks, Inconveniences and Discomforts

1) Blood Drawing: You may have some discomfort and bruising at the site of needle entry. There is a very small risk of fainting. Infection in the area of the needle insertion is rare.

2) Risks associated with MRI: People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury. They may have small metal fragments in their eye without knowing it. You will be screened for these conditions before having any scan, and if you have any, you will not receive an MRI scan. If you have a question about any metal objects being present in your body, you should inform the staff. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

It is not known if MRI is completely safe for a developing fetus. Therefore, all women of able to become pregnant will have a pregnancy test performed no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in

people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away. Please notify the investigators if you have hearing or ear problems. You will be asked to complete an MRI screening form for each MRI scan you have. There are no known long-term risks of MRI scans.

3) Risks associated with PET: Radiation exposure during the PET scan: This research study involves exposure to radiation from 2 PET scans that use a total of 24 millicuries of the [11C]raclopride, plus a small amount of radiation from the transmission scan done to calibrate the scanner. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.6 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil.

If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell us if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant, you will not be permitted to participate in this research study. If you are breast feeding, you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults are.

The radiopharmaceutical used, carbon-11 labeled raclopride, is being administered under an investigational new drug (IND) approval from the Food and Drug Administration (FDA). Peter Herscovitch, M.D. is the sponsor. The sponsor and the FDA have access to the medical records of the research subjects.

4) Risks associated with methylphenidate:
Side effects of methylphenidate may include nervousness, trouble sleeping, loss of appetite, weight loss, dizziness, nausea, vomiting, headache, or blurred vision. Side effects may include allergic reactions, heart attack, abnormal heart rate, stomach pain, stroke, mood changes, loss of hair. If any of these effects persist or worsen, tell your study coordinator or study doctor promptly. You do not have to wait until a planned visit to report adverse events. You can call 1-855-2-OnPage (or +1 (855) 266-7243 24/7 hours/day. You can the nearest emergency room in the event of life-threatening emergency.

Pregnancy: Methylphenidate has not been studied in pregnant women. We will give a pregnancy test to any woman who is able to become pregnant before enrolling her into the study. We will repeat the urine pregnancy test before MRI, PET or TMS. You will not be able to enroll in the study if you are pregnant. You are not able to have any more methylphenidate, PTEs, TMSs or MRIs if the pregnancy test becomes positive during the study.

Statement on contraception:

We do not know if the study drug affects pregnancy or fetal development. Therefore, sexually active women who are able to get pregnant must agree to use an effective method of contraception (birth control) from the time you enroll in the study until 2 weeks after you completed the study drug.

Effective methods of contraception for this study include:
1. hormonal contraception (birth control pills, injected hormones or vaginal ring),
2. intrauterine device
3. barrier methods (condom or diaphragm) combined with spermicide
4. surgical sterilization (hysterectomy, tubal ligation), or vasectomy in a partner.

It is important for you to know that no method of birth control is totally effective in preventing pregnancy except for surgical sterilization (hysterectomy or tubal ligation for women and vasectomy for men) and total abstinence from sexual relations.

Nursing mothers: It is not known whether methylphenidate goes into breast milk. As a precaution, nursing mothers cannot be in this study.

5) Neuropsychological testing: The neuropsychological tests are not harmful, but may be frustrating or stressful. We only ask that you try your best. No one performs perfectly on these tasks. You may refuse to answer any question or to stop a test at any time and for any reason.

6) Risks associated with loss of confidentiality: Any time we collect information, there is a potential risk for loss of confidentiality. We will try to keep your information confidential, but this cannot be guaranteed. If we learn that you are a danger to yourself or to others, we will have to report this to the appropriate authorities for your and others' protection.

Risks associated with TMS: TMS is a safe procedure that has been used on thousands of patients throughout the world. Most people do not find the stimulation painful, but sometimes strong contractions of scalp muscles can cause some discomfort or headache. If you find the procedure too uncomfortable, you may stop it at any time. Headaches usually go away promptly with nonprescription medication. The noise of the TMS magnet may affect hearing, so you will be fitted with earplugs to wear during TMS. Magnetic stimulation will not be done in people who have pacemakers, implanted pumps or stimulators, or who have metal objects inside the eye or skull. Please tell the investigators if you have any of these or known hearing loss. If your pregnancy test is positive, you will not have TMS. We do not know if there is any risk to you or your fetus, but we want to be careful to promote your safety.

Risks associated with computer tasks (effort task): There are no risks from the effort tasks in this study except fatigue or boredom.

Anticipated Benefits: There will be no direct benefit to you from participating in this study. However, we hope to learn more about TBI.

Right of Withdrawal and Conditions for Early Withdrawal

You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. The investigator can remove you from the study at any time if she or he believes that continuation is not in your best medical interest or if you are unable to comply with the requirements of the study.

We will send your blood samples to a repository without any information that could be used to identify you. We will not be able to destroy your samples if you choose to withdraw from this study because all identifiable information has been removed and will we not be able to tell who provided the sample.

You might be able to stay in the study even if you find out that you cannot take methylphenidate or do any of the procedures.

You can talk with or write to the study doctor if you wish to stop participating in the study.

Results from this Study The researchers will not give you the results of any research tests or evaluations. However, if information is developed from this study that may be important for your health, you will be informed when it becomes available. We will share it with your doctors at your written request.

Genetic (DNA) Testing: The genetic testing is done for research purposes only. It will not provide any information about your health or ancestry. It is our policy not to give you results of any genetic testing.

Incidental findings We will inform you about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider. We may not inform you about minor abnormalities that do not have importance for your health or well-being.

Alternatives to Participation or Treatment This study is for research only and does not replace any therapy that your own doctor is giving you. You will remain under the care of your own doctors while you are in this study. The alternative to participating in this study is not to participate.

Confidentiality To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to give out information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project if they discover child, spousal, or elder abuse or that you have an intent to hurt oneself or others which is also mandatory MD Department of Health reporting.

In addition to the voluntary disclosures listed above, if you are an active member of the military, you will not have guarantees that your information will be kept completely confidential. Typically, this refers to HIV, illicit drug use, alcohol abuse, sexual misconduct or abuse, as well as serious criminal behavior, may also be reportable.

Your study information will be kept confidential to the extent possible under existing regulations and laws, but absolute confidentiality cannot be guaranteed. Complete confidentiality cannot be promised, especially to military personnel, because information bearing on their health may be required to be reported to appropriate medical or command authorities. Future research that uses your data may lead to new commercial products, but you will not receive payment for these products. Some future studies may need your health information (such as updated information on your health) that we do not already have.

Paper records will be kept in locked rooms, or in computer files protected by computer passwords. The collected data will be accessible only by research personnel. When research results are presented, no information will be given that may reveal your identity.

This study is part of the Center for Neuroscience and Regenerative Medicine (CNRM), a joint federal program involving the United States (US) Department of Defense (DoD) and the National Institutes of Health (NIH) joining physicians and scientists from different specialties to study new approaches to traumatic brain injury (TBI) research. The CNRM network will collect de-identified clinical data, imaging data, and blood samples contributed from us and other participating centers. Members of the CNRM, Uniformed Services University, Henry M Jackson Foundation, US Department of Defense and NIH, may have access to the study data for auditing purposes.

If you choose to participate in this protocol, identifiable data collected for this study will be shared with Eric Wassermann, MD and other IRB-approved study investigators who are working on this study.

We may share your data with outside investigators or collaborators but only after all information that can identify you has been removed. This data may be used for a variety of research purposes that we may not be able to specify at this time.

Data and samples may be shared with other researchers by the sponsor (CNRM). All data and samples will have personally-identifying information removed and will be coded. The same code will be used for your data and samples whenever you participate in a CNRM study. If you participate in a CNRM study with researchers outside of NIH, those researchers may therefore be able to identify samples and data from NIH as yours. Your samples and data may also be sent to other repositories for storage or additional use. It will not be possible for other repositories to identify the samples or data as yours.

Your blood samples will be stored in secured freezers at the CNRM Biorepository. Your name and identifying information will not be on the samples; we will assign them a code. The key to the code will be kept in a separate, secure area. Once the samples and the code arrive at the CNRM Biorepository, a repository manager will be responsible for maintaining the samples and sending them to others who may use the samples for research. The samples will be stored for up to 20 years. The purpose of the repository is to store a large number of samples and related data so that we can learn more about traumatic brain injury and how to rehabilitate people who may have it. The CNRM is a federal medical research program of the U.S. Department of Defense (DOD), and DOD is the custodian of the samples. The Uniformed Services University (USU) operates the CNRM and the USU IRB reviews the repository for patient protection and receives reports from a Biorepository Steering Committee on the operations of the repository.

Dr. Wassermann is responsible for your samples here at NIH and until they are received at Dr. Diaz-Arrastia's laboratory at his CNRM laboratory for analysis pertaining to this study. Dr. Diaz-Arrastia is an outside study doctor on this study. The remainder of blood not needed for Dr. Diaz-Arrastia's analysis will be taken to the CNRM Biorepository. Your blood samples will only be accessible by current and future CNRM Investigators after approval by all relevant IRBs. Your sample

may be used for other research projects if you agree. If you do not want your sample used for other studies, please initial on the line below

_____I do not want my samples used for other research projects. Please destroy my samples once this project is complete.

If you withdraw from this research project before it is complete, any remaining samples you have contributed will be discarded. Results obtained before you withdraw will be kept and your privacy will be protected.

We may share your data, including imaging data, with outside investigators or collaborators but only after all information that can identify you has been removed. Your data, including imaging data, will be stored either at the study origination site or at the CNRM Image Processing Core database at NIH. This data may be used for a variety of research purposes including genetic research that we may not be able to specify at this time. The Henry M. Jackson Foundation for the Advancement for Military Medicine (HJF) may also access samples and data for audit purposes.

_____ I give my permission to Dr. Wassermann and the Investigators in this study to store and share my data, including imaging data, with other researchers after it has been de-identified.

_____ I do not give my permission to Dr. Wassermann and the Investigators in this study to store and share my data, including imaging data, with other researchers after it has been de-identified.

Future Contact We will send your research results without identifying information to the CNRM Informatics Repository. Your data may be used for other research projects. If you do not want your data used for other projects, please note this by initialing the appropriate space below. Your data will only be shared with approved Investigators. Any future use of the data must be approved by CNRM Repository and NIH review committees. Future research that uses your data may lead to new commercial products, but you will not receive payment for these products. Some future studies may need for health information (such as updated information on your health) that we do not already have. If so, we may contact you to obtain this information. You are not obligated to provide any additional information.

_____ I do not want my de-identified data from this study used for other projects.

_____ I am willing to share de-identified data learned about me in this study with researchers working on other studies that Drs. Wassermann and Diaz-Arrastia think are important and that my information will help.

Compensation and Travel costs You will be compensated for research-related discomfort and inconveniences in accord with NIH guidelines. If you are unable to finish the study, you will be paid for those parts completed.

Blood collection: $20.00, Neuropsychological testing including attention tests: $75.00, MRI: $50.00, each PET $50.00 ($100 for PET with placebo and with methylphenidate). TMS for both placebo and methylphenidate will be $75. Study participants may also be reimbursed for travel expenses.
$20.00 for completing or attempting to complete the blood draw
$75.00 for completing or attempting neuropsychological testing including attention tests
$50 for completing or attempting the MRI
$50 for completing or attempting the each PET ($100 for PET with placebo and methylphenidate).
$75 for completing or attempting the TMS (with placebo and methylphenidate)

Visit 1 will be compensated $70, Visit 2 $150, Visit 3 $100 and Visit 4 $145. Maximal possible compensation will be $465 for all completed 4 visits. Study participants may also be reimbursed for travel expenses.

Posting of Research Results on www.ClinicalTrials.gov

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

OTHER PERTINENT INFORMATION

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

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

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

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Building, Room, Telephone. Dr Eric Wassermann, Building 10, Room 7D43, 10 Center Drive, Bethesda, MD 20814, tel 301-496-0151

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

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative Date

Print Name

B. Parent's Permission for Minor Patient.

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

Signature of Parent(s)/Guardian Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM THROUGH.

Signature of Investigator Date

Print Name

Signature of Witness Date

Print Name