**Application for Review of Human Research:**

**IRB Protocol Summary-- Biomedical Research**

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**PROTOCOL TITLE**

***1. Full Title***

**Multi-modal neuroimaging of irritability in youth**

***2. Brief Title***

**Imaging of irritability in youth**

**STUDY SPONSORSHIP**

***1. Funding Sponsor***

NIMH R01MH107703

***2. Primary Sponsor***

Theodore D. Satterthwaite, MD, MA

**500 WORD PROTOCOL ABSTRACT**

Irritability is present in multiple disorders in youth, suggesting that it is a dimension of psychopathology that cuts across traditional categorical diagnostic boundaries. We propose to investigate how abnormal brain development produces dimensionally defined symptoms of irritability by leveraging the resources and data of the Philadelphia Neurodevelopmental Cohort (PNC). As part of the PNC, a large sample of youth ages 8-21 completed cross-sectional neuroimaging along with clinical and cognitive phenotyping, including screening questions for irritability. We will conduct multi-modal neuroimaging in 140 youth with diverse psychopathology who screen positive for symptoms of irritability and 60 matched typically developing controls. Multi-modal neuroimaging procedures that will be repeated include T1 imaging of brain structure, arterial spin labeled MRI of cerebral perfusion, a resting-state scan of functional connectivity, and a fractal version of the ­n-back working memory task. These longitudinal measures will be supplemented by the cross-sectional acquisition of sequences that are particularly relevant to irritability, including a high temporal resolution resting state sequence to examine dynamic executive-affective connectivity as well as a social affective feedback and monetary reward fMRI paradigm that recruits both the ventral striatum and the amygdala. The comprehensive assessment of brain structure and function provided by these measures will enable testing a model which posits that irritability results an evolving combination of executive deficits, affective dysregulation, and executive-affective dysconnectivity. Through the proposed multi-level analysis, this innovative research will provide a substantial advance in our understanding of the neurodevelopmental substrates of irritability.

**PROTOCOL ABSTRACT**

Irritability is present in multiple disorders in youth, suggesting that it is a dimension of psychopathology that cuts across traditional categorical diagnostic boundaries. We propose to investigate how abnormal brain development produces dimensionally defined symptoms of irritability by leveraging the resources and data of the Philadelphia Neurodevelopmental Cohort (PNC). As part of the PNC, a large sample of youth ages 8-21 completed cross-sectional neuroimaging along with clinical and cognitive phenotyping, including screening questions for irritability. We will conduct multi-modal neuroimaging in 140 youth with diverse psychopathology who screen positive for symptoms of irritability and 60 matched typically developing controls. As most subjects will have completed baseline multi-modal neuroimaging procedures, we will repeat many of these sequences, including T1 imaging of brain structure, arterial spin labeled MRI of cerebral perfusion, a resting-state scan of functional connectivity, and a fractal version of the ­n-back working memory task. These longitudinal measures will be supplemented by the cross-sectional acquisition of sequences that are particularly relevant to irritability, including a high temporal resolution resting state sequence to examine dynamic executive-affective connectivity as well as a social affective feedback and monetary reward fMRI paradigm that recruits both the ventral striatum and the amygdala. The comprehensive assessment of brain structure and function provided by these measures will enable testing a model which posits that irritability results an evolving combination of executive deficits, affective dysregulation, and executive-affective dysconnectivity. Accordingly, in Aim 1 we will delineate how longitudinal changes in brain development as measured by multi-modal imaging are associated with irritability. In Aim 2, we will demonstrate that irritability is associated abnormal affective activation and connectivity using specialized functional imaging sequences acquired at follow-up. In Aim 3, as prior work has demonstrated sex differences in the both irritability and patterns of brain development, we will examine how brain phenotypes associated with irritability differ by sex. Finally, in Exploratory Aim 4 we will use advanced multivariate pattern analysis techniques to integrate high-dimensional multi-modal imaging data and predict irritability. This proposal capitalizes on the PI’s clinical experience, expertise in multi-modal developmental neuroimaging, established collaborations, and intimate familiarity with the PNC dataset. Through the proposed multi-level analysis, this innovative research will provide a substantial advance in our understanding of the neurodevelopmental substrates of irritability.

**OBJECTIVES**

**1. Overall Objectives**

**Aim 1: To demonstrate how dimensionally defined irritability is associated with abnormalities of longitudinal brain maturation within executive and affective regions using multi-modal MRI.**

*Hypothesis 1a*: Irritability will be associated with *accelerated* longitudinal reduction of cortical gray matter and cerebral perfusion in both the executive network and regions critical for affective regulation (e.g., vMFPC). *Hypothesis 1b:* There will be a *delay* in the longitudinal maturation of executive activation in the *n*-back task. *Hypothesis 1c*: Irritability will be associated with a *delay* of longitudinal functional network segregation between the executive network and affective regions including the striatum, amygdala, and vmPFC.

**Aim 2: To use specialized functional imaging measures acquired cross-sectionally at follow-up to delineate how irritability is related to dysfunctional activation and dynamics of affective circuitry.**

*Hypothesis 2a*: Using a social affective feedback task acquired at follow up, irritability will be associated with regionally dissociable functional abnormalities. Specifically, ventral striatum responses to *positive* feedback will be *attenuated*, whereas amygdala responses to *negative* feedback will be *enhanced*.

*Hypothesis 2b:* High temporal resolution multiband resting-state fMRI acquired at follow-up will reveal that elevated levels of irritability are associated with dynamic instability in affective and executive networks.

**Aim 3: To uncover sex differences within the neurodevelopmental substrates of irritability.**

*Hypothesis 3*: Males and females will have both common and dissociable brain abnormalities associated with irritability. Dissociable effects will be observed in brain regions that show prominent sexual dimorphism in youth, including ventromedial prefrontal cortex activation and hippocampal volume.

**Exploratory Aim 4**: To define **complex multivariate patterns** of brain development that predict irritability. *Hypothesis 4a*: Multivariate pattern analysis using *both baseline and follow-up* imaging data will predict irritability at follow-up by identifying executive and affective regions that have deviant patterns of development*.*

*Hypothesis 4b*: Multivariate pattern analysis using *baseline imaging alone* will provide *prospective prediction* of irritability at *follow-up.*

*Hypothesis 4c:* Due to sex differences in brain development, sex-stratified models will provide more accurate prediction of irritability.

**Primary Outcome Variables**

Here we explore a range of metrics of brain development including brain structure, perfusion, functional connectivity, executive system activation, and amygdala responses.

**Secondary Outcome Variables**

Secondary outcome variables will consist of novel multivariate summary measures of high-dimensional neuroimaging data.

**Background**

Irritability in youth is the target of increasing research as evidence regarding its impact mounts. Symptoms of irritability include abnormal mood, markedly exaggerated responses to negative stimuli, and limited frustration tolerance. Notably, while many youths with chronic irritability are diagnosed with bipolar disorder in the community, studies utilizing careful assessment and longitudinal follow-up have demonstrated that non- episodic irritability is a distinct phenotype from bipolar disorder. Nonetheless, high levels of irritability are associated with equivalent levels of functional impairment as other major mental illnesses, including reduced income and educational attainment. Importantly, symptoms of irritability are present in many categorical DSM diagnoses, suggesting that it may be an important dimension of psychopathology that spans traditional diagnostic boundaries. This conceptualization is supported by work showing that symptoms of irritability exist on a continuum, and can be measured reliably as a unique symptom dimension. Despite recent research, the neurobiological substrates of irritability are only beginning to be described.

Convergent evidence from several studies points to inter-related structural and functional abnormalities within the brain’s executive and affective systems. For example, a recent fMRI study using a frustrating attention paradigm found that irritable youths had deficits in attention, higher levels of frustration, and diminished activation in a network of executive regions as well as limbic structures including the amygdala and striatum. Further evidence for limbic dysregulation was provided by Brotman et al., who demonstrated that irritable youths had diminished activation of the amygdala when rating fear in neutral faces. In a separate study, disruptive youths who had high levels of irritability demonstrated abnormalities in reward prediction errors in the striatum. These functional neuroimaging studies delineate abnormalities of the brain’s executive system in addition to dysfunction in regions critical for affective processing including the amygdala and striatum. Areas of volume loss from structural neuroimaging studies have been found in regions that partially overlap with these functional abnormalities, suggesting that such circuit-level changes may be related in part to developmental abnormalities in structural brain maturation. To our knowledge, however, there has been only one longitudinal study examining evolving structural abnormalities in irritable youths, which reported volume loss in fronto-striatal regions that were distinct from changes seen in bipolar youths.

Taken together, these findings suggest that a constellation of inter-related maturational deficits in the brain’s executive and affective systems produce irritability, and formed the foundation of a model proposed by co-investigator Ellen Leibenluft. However, longitudinal studies of irritable youths are quite sparse, limiting inferences that directly relate irritability to development. This gap is critical as understanding how aberrant patterns of brain development predispose youths to symptoms of irritability is a prerequisite for the development of precision medicine, including early interventions that “bend the curve” of development in order to achieve better outcomes. Accordingly, here we propose a research plan that will describe how abnormalities of brain development as characterized by multi-modal neuroimaging are associated with dimensionally defined symptoms of irritability in youth with diverse psychiatric diagnoses. To do this, we will conduct follow-up neuroimaging and irritability phenotyping in a sample of youths previously imaged as part of the Philadelphia Neurodevelopmental Cohort (PNC), a large-scale study of brain development that included cross-sectional multi-modal neuroimaging and clinical phenotyping, as well as additional youths who screen positive for irritability.

Preliminary analyses of imaging data from PNC participants who screened positive for irritability at baseline lends support for the existing model but also suggests specific extensions. As described in further detail below, irritable PNC youths demonstrate hypo-activation of executive regions during a working memory task. Additionally, irritable PNC youths have volume loss and hypo-perfusion of the ventromedial prefrontal cortex (vmPFC), which is known to be critical for affective regulation and has prominent connections with the amygdala. Furthermore, consistent with prior work, preliminary data from a social affective feedback task demonstrate that irritable youths have diminished differentiation of responses to positive and negative social feedback in the striatum. Finally, resting-state connectivity analysis of baseline PNC data provides evidence of dysconnectivity between executive regions such as the anterior cingulate and default mode regions implicated in affect regulation such as the vmPFC, consistent with a breakdown of the normal segregation between executive and affective brain networks. Based on this preliminary data, here we propose an expansion of the existing model whereby regionally distinct abnormalities in executive and affective circuitry interact to produce changes of large-scale network topology and stability that promote irritability.

**Study Design**

**Phase**Not Applicable.

**Design**

This is primarily a follow-up study to our large population-based Philadelphia Neurodevelopmental Cohort study (protocol #810366). We anticipate that the majority of subjects recruited for the present study will have been previously enrolled in study #810366 and provided consent to be re-contacted for future research. Subjects will also be recruited from other subsequent protocols associated with protocol #810366, including protocols #810336, #816281, #815814, #818621, #816275. We anticipate that most subjects who did not participate in one of these protocols will be recruited through the Neuropsychiatry Program’s IRB approved center-wide assessment protocol #813943. For those research subjects who have provided consent to be re-contacted and have expressed a continued desire to participate in future research studies, coordinators across the Center may utilize the department database to recruit these individuals for a new study. Coordinators receive database access only through PI approval and after completed training with department Data Management. As described in the Neuropsychiatry Section’s center-wide protocol (#813943), the department database is encrypted and password protected. Should a subject indicate he/she is no longer interested in volunteering for research studies his/her study ID is labeled as non-active. This non-active field will prevent non-active study ID’s from appearing in database queries and also prevent inadvertent contact by future coordinators. In order to facilitate recruitment of subjects with a history of mood disorders, (a sample of the population that can be difficult to recruit based on our experience from approved protocol #810211), patients meeting inclusion criteria may be directly recruited from the University of Pennsylvania Behavioral Health Clinics at 3535 Market street, and IRB approved recruitment flyers may also be placed outside mood disorder clinics at that location.

As part of the prior studies, subjects have received standard clinical and cognitive phenotyping. Here, we propose to follow up a subset of adolescents and young adults for detailed phenotyping of irritability. Nearly all subjects will have received a detailed diagnostic interview as part of protocol #810366 or #813943. However, a minority of subjects who have not received this diagnostic interview will be asked to complete a full diagnostic interview instead of a follow-up update, using identical procedures to protocol #810366 or using the standard procedures outlined in the Neuropsychiatry Program’s common assessment protocol (#813943).

In order to specifically evaluate irritability within the context of ongoing brain development, we propose to dimensionally assess irritability and associated brain imaging in a sample of youths who screened positive for symptoms of irritability, as well as matched typically developing comparators. To examine executive dysfunction, we will utilize a fractal n-back working memory task, and affective-executive connectivity will be examined using longitudinal resting- state functional connectivity data sampled at standard temporal resolution (3s). Both prior work and our conceptual model emphasize the importance of affective and reward systems, which will be probed with a novel social affective feedback task and a monetary reward task which robustly recruit both the ventral striatum and amygdala. Furthermore, we will use ultra-high temporal resolution (0.5 s) multiband imaging to test for dynamic instability of interactions between executive and affective circuits. In response to accumulating evidence of the importance of sex differences in brain development, we will investigate whether brain abnormalities in affective circuits associated with irritability diverge between males and females. Multi-modal neuroimaging data will be integrated using advanced multivariate pattern analysis techniques to predict irritability.

**Study Duration**

This is projected to be a 4-year study, with start date contingent upon IRB approval and an end date of July 1, 2019.

**Resources necessary for human research protection**

All staff has extensive experience with the studies being proposed, and all will be trained on the procedures of the current study. All physicians (Drs. Satterthwaite & Wolf) have extensive experience with patients with psychiatric disorders and implementing research designs of similar or greater magnitude. Research assistants working on this project will have experience in administering rating scales and behavioral testing. Assessment and training outside of MRI are performed in the Brain Behavior Laboratory located within the Neuropsychiatry Section of the Dept. of Psychiatry on 10th Floor Gates Building at HUP, which will provide excellent facilities for this research.  There is a reception area, intake and examination rooms for daily operations. The proximity to the General Clinical Research Center and the laboratory facilities (e.g., Brain Behavior Laboratory, Neuroimaging) is optimal for research interactions and enhances our ability to have participants undergo multiple protocols. Data management is provided by the Data Core of the Brain Behavior Laboratory. This includes subject tracking, database management, data entry, data validation and quality assurance.

**Target population**

Subjects will primarily be recruited from the pool subjects who completed baseline neuroimaging and clinical assessment as part of the Philadelphia Neurodevelopmental Cohort (PNC), a large-scale neuroimaging study of youths ages 8-21. Subjects will be recruited in two groups, including youth who have diverse psychopathology and symptoms of irritability. Typically developing comparators matched on age, sex, and race will also be enrolled in order to establish normative longitudinal developmental patterns. Median time to the follow-up imaging session from prior protocols will be 4-5 years; feasibility of longitudinal follow-up is ensured through an established recruitment and follow-up infrastructure.

Subjects may also be recruited from the large pool of interested participants as part of the Neuropsychiatry Program’s center-wide protocol, which provides the Neuropsychiatry Program with common procedures including recruitment, screening, and clinical assessment. Please refer to this protocol, #813943, for a complete description of all subject accrual procedures. Participants recruited through the center-wide protocol will receive a baseline irritability phone screen to assess for eligibility into one of the two study groups. Finally, as noted above, patients with mood and anxiety disorders and symptoms of irritability may be recruited from outpatient clinics at 3535 market street.

**Subjects at Penn**

200

**Subjects at Sites other than Penn**

0

**Accrual**

Subjects may be recruited from the pool of subjects who completed baseline neuroimaging and clinical assessment as part of the PNC (#810336). Subjects may also be drawn from a large pool of subjects who have agreed to be contacted for research as part of our Neuropsychiatry Program’s center-wide protocol (#813943). The latter protocol provides the Neuropsychiatry Program with common procedures including recruitment, screening, and clinical assessment. Please refer to this protocol, #813943, for a complete description of all subject accrual procedures.

Subjects will be recruited in two groups, including youth who endorsed symptoms of irritability in the context of a psychiatric diagnosis at baseline assessment or via a baseline irritability screen. Typically developing comparators matched on age, sex, and race will also be enrolled in order to establish normative longitudinal developmental patterns. Analyses of basic demographics characteristics will be conducted every six months; prominent differences among the groups in any demographic variable will lead to adjustments in recruitment strategies to balance out the groups. The ethnicity of the pool of subjects in protocol #810336 and #813943 reflects the local community and that balance will be maintained in the current study.

**Key inclusion criteria**

Irritable youths: Irritable youths must meet criterion a *AND* b *OR c*

a. Met criteria at baseline for at least one categorical DSM-IV diagnosis, including ADHD, ODD, conduct disorder, or any mood, anxiety, or psychotic disorder.

***AND***

b. Positive screen for one or more of the items assessing irritability on baseline assessment through participation in prior protocols.

***OR***

c. Symptoms of irritability by clinician assessment or self-report.

Typically developing youths:

a. No DSM IV axis I diagnosis.

All subjects:

a. Gender: Males and Females.

b. Age: 11-25. This age range allows us to focus on the critical period of adolescence and young-adulthood.

c. For MRI studies, women of child bearing potential must have a negative urine pregnancy test at screening and each test visit.

d. Proficiency in English, as study assessments and tasks are designed for English speakers.

e. Able to understand study procedures and agreeing to participate by giving written informed consent.

**Key Exclusion Criteria**

All subjects:

a. Any metallic implants, claustrophobia, or other contraindications to MRI.

b. Significant medical or neurological illness that in the PI’s judgment may increase risks of the study, significantly effect brain function, or impede participation.

c. Pregnancy (negative urine pregnancy screen required).

d. Any history of pervasive developmental disorder or mental retardation.

e. Non-psychiatric medical disorders that may impact brain function or visual acuity.

f. Acute intoxication with alcohol or other substances based on clinical assessment, subject report, or results of laboratory testing.

Current nicotine use and past substance use will be assessed and their effects examined with covariate and sensitivity analyses.

Typically developing youths:

a. Current symptoms of any Axis I psychiatric disorder.

b. Current use of psychoactive medications to treat ongoing symptoms that are gauged by the investigators to interfere with interpretation of study results.

c. Any history of a personality disorder.

d. Presence or history, in subject’s first-degree relatives, of schizophrenia, schizoaffective disorder, or bipolar disorder.

Note: Race, ethnic origin, or economic status will not be considered in selection of study participants, and the distribution will therefore reflect the diverse population found in the surrounding community.

**Vulnerable populations**

Participants will meet with a trained Research Coordinator who will explain the research and its goals. For minors, the process includes the child and the parent(s). After full explanation of all the research procedures and reading the consent form, informed consent will be obtained from the participant; however, if there is reason to suspect that the participants mental state is impaired enough to cast doubt on the validity of the statement of consent, they will not participate. For participants ages 11-17, assent will be obtained from the child/adolescent in addition to parental consent and permission. Research staff will review the informed consent document section by section with each prospective participant. For minors, this process will be done in the presence of the parent or guardian. Participants will be given the option of reading through the document himself/herself, or having it read to him/her, as an initial step toward explanation of what participation entails. Participants’ questions will be answered throughout. The research staff person will take care to explain fully the following issues: the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, and the steps to be taken to protect confidentiality of information.

**Subject recruitment**

Subjects will be primarily drawn from a large pool of subjects who have agreed to be contacted for follow-up research as part of our large population based study of neurodevelopmental genomics (protocol #810336) or from the Neuropsychiatry Program’s center-wide protocol (#813943). In addition, subjects will be recruited from other protocols, including protocols #810336, #816281, #815814, #818621, #816275. Subjects who participated in these protocols indicated their willingness (or lack of) to be re-contacted for further research. We will preferentially recruit from subjects who have received detailed follow-up clinical phenotyping and baseline neuroimaging as part of those protocols. Given that detailed clinical information will already be available for these subjects, we will use abbreviated phone-screening procedures for subjects who have completed this part of the study (see Procedures, below).

We will also utilize recruitment flyers placed on approved bulletin boards outside the Mood and Anxiety Disorders Research Clinic at 3535 Market Street. Locations for flyer placement may also include the table in the waiting area of the Mood and Anxiety Disorders Research Clinic, the bulletin boards by the elevators in the lobby outside this clinic, and the bulletin boards located by the 2nd Floor Outpatient Psychiatry Center. These subjects will receive more detailed phone pre-screening for irritability symptoms, eligibility for MRI, and symptoms of mood/psychiatric disorders (see Procedures, below).

In addition, we will utilize iConnect, which is a novel clinical trial-matching technology designed to make web searches by potential research subjects easier, allowing for faster and more efficient recruitment. Research assistants will be trained on the new interface and will implement this technology to increase recruitment efforts. Potential subjects will be instructed to contact the main study coordinator and will receive more detailed phone pre-screening for irritability symptoms, eligibility for MRI, and symptoms of mood/psychiatric disorders (see Procedures, below).

All subjects will be contacted by phone (or email if the subject indicates that as a preferred method of contact) and informed of the research opportunity. A trained coordinator will use the IRB-approved scripts for this recruitment call/email. Separate phone and email scripts exist for subjects who have previously received detailed clinical assessment and baseline neuroimaging and those who have not. These scripts are based upon the IRB-approved scripts from protocol #810336 (see attached). Phone scripts include templates for follow up and confirmation calls. A template reminder email that may be sent to subjects is also attached.

We may contact subjects in the future in order to maintain up-to-date demographical information. In addition, if new studies in the Brain Behavior Laboratory are applicable to subjects, they may be asked to participate. A trained coordinator will use the IRB-approved scripts for this follow-up contact as detailed in the Neuropsychiatry Section’s common, center-wide protocol (#813943). This follow-up evaluation is optional and subjects will have the opportunity to indicate their preference regarding follow-up contact on the Neuropsychiatry Section’s IRB approved center-wide intake consent form (#813943). Subjects may be contacted annually or bi-annually.

**Subject Compensation**

The majority of subjects recruited to this study will have already had detailed clinical phenotyping performed as part of protocol #810336, and therefore only participate in a one-day visit including additional irritability phenotyping and neuroimaging. However, a minority of participants may not have received standard psychiatric phenotyping, and therefore will also receive a standard diagnostic interview as part of an initial study visit, with neuroimaging occurring on a separate second day. This will only occur for subjects who have not already received that diagnostic interview as part of study #810336 or #813943.

We plan to implement the new Greenphire ClinCard system as subject’s method of payment. The ClinCard is a reloadable prepaid card that gives individuals the option to use the card as a debit or credit card, withdraw funds at an ATM, or obtain a cash advance at a bank. At the end of the study visit, the study coordinator will transfer the money onto the card. All payments over $100.00 will be paid by ClinCard. If a subject receives $100.00 or more for his/her participation in this study on one day, he/she must provide his/her full Social Security Number. Additionally, the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that is $600 or more during one calendar year. Subjects will be fully informed of this new payment method during the phone screen.

For subjects paid via ClinCard. We will provide a subject with one free replacement ClinCard if it is lost or stolen. If more than one loss occurs, a $3.00 fee will be incurred from the subject's remaining card balance. A $3.00 fee will be incurred if the Clincard is not used for any purchase or withdraw within 6 months. For subjects under 16 years old, when receiving the ClinCard, during consenting, the study coordinator will strongly encourage the parent to discuss the use of the card with their child and assist him/her with all transactions or withdrawals. In addition, study coordinators will inform parents to help their child maintain the card in a secure location.

Day 1: Psychiatric and Cognitive Assessment

For such participants who previously have not received a detailed psychiatric interview, payment for the first assessment day will follow the payment structure detailed in the center-wide protocol at the Neuropsychiatry Section. The Neuropsychiatry Section utilizes a common, center-wide protocol as noted above in this protocol (IRB# 813943). Subject compensation for the clinical assessment, neurocognitive battery and genetic blood sample activities for this protocol will be as follows and described below:

* $40 for the Clinical Evaluation/Assessment (3 hours)
* $40 for the Computerized Neurocognitive Battery (1 hour)

A urine sample is collected in order to test for recreational or street drugs. A breath test/saliva swab may be used to check for alcohol intoxication. A positive drug screen may be exclusionary. If a subject appears intoxicated at the time of the visit or tests positive for alcohol or other substances, we will not continue with the study enrollment procedures and he/she will be paid $10 for their time and travel.

Subjects will also be reimbursed for travel expenses (transportation and parking).

Day 2: Neuroimaging

For the majority of subjects who only participate in the neuroimaging part of the study, payment will be a combination of a flat payment of $100 in addition to a variable payment based on the choices made during tasks which use monetary rewards which are used to examine brain reward system function. Additional compensation will range from $0-15. This amount is deemed to provide some compensation for time, travel and discomfort, without being coercive. The purpose of any additional compensation is to increase task engagement and provide an incentive to answer the questions on the task truthfully. Such incentives are common in economic and decision-making research, and are often required in order to publish research results in economics journals. For example, if the experimental task involves choosing between two rewards, we will randomly choose one trial from the task and pay the subject whichever option they picked. Subjects will also be given ample opportunity to ask questions about these payments. The details of any additional compensation, and how this compensation depends on the task, will be thoroughly explained to the subject before they begin the study, and the experimenter will test the subjects' understanding of this process. Subjects will also be given ample opportunity to ask questions about these payments. Subjects will be reimbursed for travel (transportation and parking) expenses.

**Procedures**

The study involves several segments, the procedures for which are addressed separately here.

1. Pre-Study Screening and Recruitment Procedures

Potential participants will be recruited and screened using procedures adapted from protocol #810336 and #813943. Abbreviated pre-study screening procedures will be used for subjects who have already received clinical assessment and baseline neuroimaging as part of that protocol. For subjects who have not received detailed clinical assessment and baseline neuroimaging, a more detailed phone pre-screening for both eligibility for MRI as well as symptoms of irritability will be used. As detailed in the attached phone script, subjects (if 18 years old) or their parent or guardian (if under 18) will be asked about past psychopathology symptoms.

Baseline irritability screening: At baseline, trained assessors performed clinical phenotyping using a highly- structured computerized diagnostic interview based on the K-SADS. The baseline assessment included four items that provided a screen for irritability. These items were from the depression, bipolar disorder, and oppositional defiant disorder sections of the interview, including such questions as “Are you often irritable or grouchy, or do you often get angry because you thought that things were unfair?” Follow-up questions ensured that symptoms were not present only within a mood episode. While these questions do not provide specialized assessment of irritability, they do provide a screen for irritability. Inclusion criteria will require that subjects have at least one categorical DSM diagnosis and also endorsed one of the four irritability items. Requiring threshold-level symptoms for another diagnosis enhances the clinical relevance of the research and obviates the possibility of studying individual differences in irritability in a healthy sample. Undoubtedly, this group includes youths with a broad range of irritability, facilitating dimensional analyses.

For those subjects who did not receive the baseline irritability screening, they will be asked the irritability screen on the phone during the pre-study screening process. As with the subjects recruited through the PNC, additional subjects must endorse one of the four irritability items found in the baseline assessment. These participants will be asked additional questions on psychopathology to determine if they will be likely to have at least one categorical DSM diagnosis.

Following pre-screening, as in protocol #810336, subjects will receive a reminder call 1 week and 1 day before the appointment, as well as a reminder email or letter. For details please see the attached documents.

2. Standard Psychiatric and Cognitive Assessment

As noted above, the majority of subjects recruited to this study will have already had detailed clinical phenotyping performed as part of protocol #810336 or #813943, and therefore may only need to participate in a one-day visit including additional reward phenotyping and neuroimaging. However, a minority of participants may not have received standard psychiatric phenotyping, and therefore will also receive a standard diagnostic interview as part of an initial study visit, with neuroimaging occurring on a separate second day. This will only occur for subjects who have not already received that diagnostic interview. Psychiatric and cognitive assessment will occur at the Schizophrenia Center, Neuropsychiatry Section, 10 Gates Pavilion at the Hospital of the University of Pennsylvania. Participants who will only take part in the behavioral section of the study will have separate abbreviated assessment procedures (see below). Participants deemed eligible based on preliminary screening will, after providing consent, complete assessment procedures designed to confirm eligibility, establish diagnoses, and characterize relevant phenotypes. The total time for these assessments and other procedures ranges from 3-6 hours, depending on participant factors. The assessment procedures in the Neuropsychiatry Section’s center-wide protocol #813943 include medical, neurological, psychiatric, substance use, personality, cognitive, and psychosocial evaluations. Details about these procedures are described in that protocol #813943. For all studies, participants will be asked at the end of the intake and assessment session whether they would like to be informed about future studies in which they may participate. It will be made clear to participants that this is entirely voluntary and that they will receive full compensation for time already spent participating in the study regardless of whether they agree to be contacted about future research opportunities. This personal information will be kept securely and stored separately from the participants' data. Protocol #813943 allows for detailed psychiatric assessment, dimensional measures of psychiatric symptoms, and standard measures of neurocognition. Please see that protocol for further details. Relevant consent documents are attached.

Irritability phenotyping: The primary measure of irritability will be the Affective Reactivity Index (ARI), developed by co-investigator Dr. Leibenluft, which has been shown to provide a reliable, fully dimensional measure of irritability. Both the self-report and parent-report ARI will be administered for minors. For comparison to the ARI, additional irritability phenotyping will be provided via the state-trait anger expression inventory (STAXI).

Diagnostic assessment. Although this proposal focuses on the dimensional assessment of irritability, subjects may receive a detailed diagnostic assessment (SCID) or a computerized version of the K-SADS interview.

Additional symptom assessments: In addition to irritability, we will also assess other dimensions of psychiatric pathology. Symptoms of depression will be assessed using the Montgomery-Asberg Depression Rating Scale and the Beck Depression Inventory II. Hypomania and mania will be assessed with the self-report Hypomania Checklist and the Young Mania Rating Scale interview. Anxiety will be assessed using the State-Trait Anxiety Inventory and the Screen for Child Anxiety Related Emotional Disorders. Aggression will be assessed using the Reactive-Proactive Aggression Questionnaire.

Moreover, as in protocol #810211, these measures may include, but are not limited to, standard instruments such as: the Clinical Assessment Interview for Negative Symptoms (CAINS, formerly called the NSRS), the Chapman Trait Anhedonia Scales for physical (RPAS) and social (RSAS) anhedonia, the Structured Interview for Schizotypy (SIS) (which is contained within the DIGS), the Drug Attitude Inventory (DAI-10), the Hollingshead SES Scale, the Positive and Negative Affect Schedule (PANAS). Anxiety will be assessed at intake and on the day of fMRI (before and after scanning) using the State-Trait Anxiety Inventory (STAI), and additionally the Beck Anxiety Inventory (BAI). The Fagerström Test for Nicotine Dependence (FTND) will be used to measure nicotine dependence severity. Gambling will be assessed using a variant of the South Oaks gambling screen. One or more of the following scales will be used to assess depression: Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI), the Montongomory-Asberg Depression Rating Scale (MADRS), and the Calgary Depression Scale for Schizophrenia (CDSS). Manic symptoms may be assessed using the Young Mania Rating Scale (YMRS) and/or the Clinician-Administered Rating Scale for Mania (CARS-M). Additional measures of mood may be assessed using the Bipolar Inventory of Symptoms Scale (BISS) and the Mood Disorder Questionnaire (MDQ). Additional measures of reward/motivation may be used including: the self-report Behavioral Activation/Inhibition Scales (BAS/BIS); the Brief Sensation Seeking scale (BSS); the self-report Temporal Experience of Pleasure Scale (TEPS); the Future Events Task (FET), and the self-report Domain-Specific Risk-Taking scale (DOSPERT). Other standard psychological scales may be administered as well.

Cognitive assessment. All subjects will complete a comprehensive cognitive assessment using the Penn Computerized Neurocognitive Battery (CNB), which assesses a broad range of cognitive domains.

Decision-making battery: Reward-related decision-making sits at the intersection of executive and affective systems that we hypothesize are important for the pathogenesis of irritability. In particular, certain decision- making tasks that require restraint of affective systems through executive function are especially likely to be impaired in irritable youths. Such impairment is relevant, as impulsive decision-making is known to be related to a range of negative outcomes associated with risk-taking behavior such as drug use, pregnancy, accidental injury, and violence. Building on a long-standing collaboration with UPenn psychologist and behavioral economics expert Dr. Joseph Kable, we will assess decision-making using both a standard delay discounting task that assess delays over longer periods (days-months), as well as a recently-validated “willingness to wait” paradigm that examines delays of seconds-minutes in real time. As noted in our conceptual model, we expect impulsive decision-making will relate to imaging measures of affective-executive network interaction. Furthermore, as in protocol #808799 a computerized progressive ratio reinforcement task may be used to provide an objective measure of each subject’s motivation for monetary or types of rewards. This task requires the subject to perform increasing repetitions of an easy, attention-requiring task in order to obtain decreasing levels of reward. Each subject’s ‘motivation’ will be quantified as the ratio of effort (maximum number of repetitions) to reward value.

3. Neuroimaging Protocol

As noted above, most subjects will have already had standard psychiatric phenotyping completed at the time of enrollment in this study, and the procedures outlined in section #2 (above) will not apply. However, all subjects enrolled in this current study will participate in a 1-day (approximately 5-hour) visit where detailed measures of irritability will be obtained through additional clinical scales and interviews focusing on anhedonia, reward decision-making paradigms, and neuroimaging. These additional procedures have all been used as protocols #810336, #816281, and #810211 and adapted to the adolescent population of the present study.

Preparation for MRI: A brief (5 min) practice task will be conducted inside a decommissioned MRI scanner as part of a mock-scanning session in order to ensure all subjects understand and can perform the task, as well as to acclimatize the subjects, reducing novelty and anxiety responses inside the scanner. Participants will then be prepared for scanning by the investigator and the MRI technician. After assessing state anxiety with the STAI and mood symptoms with one of the above scales, subjects will be placed supine in the scanner, wearing earplugs to muffle noise. Head fixation will be ensured by foam rubber mounted on the headcoil, which we have found provides excellent motion control even in motion prone individuals. Stimuli are rear projected (www.pstnet.com/products/BrainLogics) to the center of the visual field and viewed through a mirror mounted on the head coil. Participants are given a color-coded response device made of non-ferromagnetic components (FORP™ Current Design Inc., Philadelphia, PA), identical to that used during the practice.

Image Acquisition: Structural and functional scans will be obtained in a single session on a clinically-approved 3 Tesla Siemens Prisma (Erlangen, Germany) scanner, equipped with 80mT/m gradients and 200 mT/m/s slew-rates.  RF transmission will use a quadrature body-coil, and reception will use a Siemens receive-only 64-channel head coil. The total time in the scanner will be approximately 1 hour. Based on our experience, this is well within patients’ ability to tolerate the scanning procedures without discomfort and without excessive motion. We will acquire structural images, perfusion images, and functional images as follows; all MRI imaging will be reviewed and approved by CAMRIS.

High-resolution Anatomical Images: A 5 min. magnetization-prepared, rapid acquisition gradient echo (MPRAGE) image is acquired, which includes an inversion-recovery preparation period to produce T1-weighted contrast, and has a 1x1x1mm voxel size. The MPRAGE is used to screen for gross anatomical abnormalities, to facilitate registration of lower resolution functional images into a standardized space, and to allow identification of between-group or inter-individual variation in volume of regions that could affect interpretation of functional results.

Resting Perfusion Images: A ~5 min. pulsed arterial spin labeled (ASL) perfusion MRI and ~1.5 min. reference scan are acquired to directly measure resting cerebral blood flow, using magnetically-labeled blood as an endogenous non-invasive tracer.

Functional Images: Functional scans lasting ~45 minutes during which time the subject will be asked to perform psychological tasks described above. fMRI will be acquired with blood oxygenation level dependent imaging (BOLD) using a whole-brain, single-shot gradient-echo (GE) echo-planar (EPI) sequence. The BOLD sequences include on-line geometric correction for spatial distortions due to magnetic field inhomogeneity using a magnetic field map acquired with a 2 min reference scan. Resting-state sequences measuring functional connectivity in the absence of task conditions will be acquired as well.

fMRI Tasks: During functional MRI runs, subjects will perform a nonsocial monetary feedback guessing task and a social feedback-guessing task, both designed to evaluate the function of reward processing brain regions including ventral striatum. In the nonsocial monetary guessing task, subjects will guess whether a hidden playing card contains red or black numbers, and receive written feedback of a correct guess with a monetary win, or an incorrect guess with a monetary loss. The order of win and loss trials is pseudorandomized with an identical sequence for each subject and an equal net positive outcome equivalent to a 50% success rate. As monetary values for wins are slightly larger than monetary values for losses, subjects expect and achieve a net gain over the experiment, avoiding task frustration. The social feedback guessing task is similar, but here the subjects make a guess about a face and receive feedback either by that face appearing with a happy facial expression (positive social feedback) or an angry or sad facial expression (negative social feedback). Face stimuli are color photographs of different individuals displaying easily recognizable emotions, previously validated in control and schizophrenia subjects performing an emotion identification task.

Participants will also perform a fractal version of the n-back working memory task similar to what was completed as part of the neuroimaging protocol in study #810336.

Post-scan procedures: Subjects will rate their level of interest, effort, and emotional response to the tasks. The STAI will be performed after scanning; certain affective scales may be repeated as well.

**Statistical analysis**

*General*: Data management is provided by the Data Core of the Schizophrenia Research Center. This includes subject tracking, database management, data entry, data validation and quality assurance. Throughout the study data verification will be performed to ensure the data set's validity and integrity. This is most important for variables that are not ascertained in electronic form. Electronic data including imaging and behavioral data will be examined manually and automated quality assurance (QA) algorithms to assess such factors as adequate behavioral performance, in-scanner motion, and signal-to-noise ratios. Statistical analysis will be done in consultation with a biostatistician. Study participants will be characterized on demographic variables, clinical phenotype variables, neurocognitive variables, task performance variables, and regional fMRI activation measurements. Separate characterizations will be done for each group, as well as for male and female subgroups. Continuous variables will be summarized by the mean, standard deviation, 95% confidence interval, median, and range. Continuous variables first will be plotted to assess the validity of a normality assumption, identify potential outliers, and assess heteroscedasticity between groups. Where continuous variables to be considered as outcome variables cannot reasonably be considered normally distributed, transformations (e.g. square root for skewed data) to achieve an approximate normal distribution will be explored or nonparametric statistics will be utilized as appropriate. Categorical variables, nominal and ordinal, will be summarized by frequencies.

**Subject level image processing:**

*T1 imaging***:** T1 images are processed with a cutting-edge pipeline including multi-atlas skull-stripping as well as multiplicative bias correction and tissue segmentation. Using specialized longitudinal processing procedures (see below), images are registered with a highly accurate deformation that employs attribute-matching and mutual salience weighting (DRAMMS), producing volumetric RAVENS maps that are superior to standard VBM techniques. Striatum and amygdala volume and shape will be measured using FSL’s FIRST utility.

*Perfusion image processing***:** ASL data are processed using ASL toolbox to produce a cerebral blood flow (CBF) map for each subject. As T1 relaxation time is known to change in development and can bias quantification, each subject’s T1 will be adjusted using an age- and sex-specific model.

*Task fMRI***:** Subject-level time series analysis will utilize FSL. The contrast map of interest in the fractal *n*- back task is the 2-back vs. 0-back. In the social affective feedback task, we will examine positive feedback, negative feedback, and their contrast.

*Resting-state fMRI processing:* Simultaneous to two other independent groups, we identified the confounding influence of motion on rsfc-MRI data, which is of particular concern in developmental samples. Using PNC data, we developed a validated pre-processing pipeline to minimize the influence of signal artifacts related to subject motion. Pre-processed time series are extracted from a system of 264 nodes that have previously been mapped to 13 known functional brain networks, forming a network of 34,716 unique edges. Functional connectivity within this network is defined as a wavelet based coherence between regional time series in a low frequency band (0.01-0.08 Hz) that is relatively unaffected by physiological artifacts.

**Longitudinal image registration procedures:**  We will use a validated longitudinal processing approach that has substantial advantages over traditional image processing techniques. This procedure minimizes bias in estimation of longitudinal data and enhances sensitivity for detection of clinically important changes. As prior work has demonstrated that use of a template image that does not fit the study sample (e.g., an adult atlas in a study of youth) can systematically bias results, a custom population template will be created. Additionally, for each subject we will create a subject-specific T1 template (T1-SST) for use as an intermediate step in longitudinal processing to eliminate bias between study time points. Registration from each time point’s T1 image to both the T1 SST and from the T1 SST to the custom population template will use DRAMMS. Co- registration of the other imaging modalities (ASL, DTI, BOLD) to the T1 image will use boundary-based registration with integrated distortion correction using FSL’s FUGUE utility. All modalities will be mapped smoothly to template space using only one interpolation by concatenating all transforms.

**Subject Confidentiality**

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

Whenever feasible, identifiers will be removed from study-related information.

Other *(specify):* See text below.

Prior to administering the Initial Participant Screening Form, potential participants are made aware that they do not have to answer any questions that they do not wish to answer, and that they may stop the screen at any time. When a participant is enrolled in the study, he/she will be assigned an individual study identification number, at the conclusion of preliminary screening for eligible subjects.

This number will be used to label all private research information, including clinical assessments and biomaterials. Personally identifying information (e.g., name, address) will be stored apart from private information in secure physical files and electronic databases. Private information will likewise be stored in secure, separate physical and electronic locations. A linkage code connecting participant’s personal identifiers to assigned study numbers will be created. This linkage code will be accessible on an as-needed basis only to study investigators and their staff, and will be stored separately from participants’ private information and personal identifiers.

Basic demographics and test data collected are transferred in encrypted format to a secure server. Access to the server is through a password-protected account that allows access to data collected only to the investigator and their designees.

In any publication or presentation resulting from this research, the participants will not be identified.

Individuals who are currently in psychiatric treatment will continue to receive care from their current mental health provider.

**Subject Privacy / Protected Health Information**

The Schizophrenia Research Center does not initiate first contact with subjects. All subjects are referred by community mental health centers, individual physicians or through community advertisements. Subjects then phone in to the Center to express their interest in research participation. All interactions with study staff occur in private testing rooms or staff offices within the Neuropsychiatry Program located at HUP on the 10th floor of the Gates Pavilion. All subjects provide consent to be re-contacted at a later date for participation in another Center study. Subjects who consent to be re-contacted are identified as active in the Center database (described above). When a subject states he/she no longer wishes to be contacted for future study recruitment, he/she is identified as non-active in the Center database. This non-active status eliminates subjects from database queries and alerts study personnel to not contact this individual. Procedures are in place for protecting the privacy of participants. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). When a subject is enrolled in a Center study, he/she is assigned a unique identification number that is used to identify all data associated with that person, including hard copy, biological data (e.g. blood sample), and computerized data. Research data pertaining to specific subjects that is entered into computer databases is de-identified and entered under a 5-digit number that is randomly assigned rather than being connected to any PHI that would directly identify the subject. In any disclosures of study results outside of the University of Pennsylvania Health System and School of Medicine, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law or court order. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

**Data Disclosure**

Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, except as may be required by court order or by law, such as, but not limited to, the presence of a harmful situation to the participant or others and/or the abuse of a child.

**Informed Consent Procedures**

Participants will meet with a trained Research Coordinator who will explain the research and its goals. The process includes the child and the parent(s). After full explanation of all the research procedures and reading the consent form, informed consent will be obtained from the participant; however, if there is reason to suspect that the participants mental state is impaired enough to cast doubt on the validity of the statement of consent, they will not participate. For participants ages 11-17, assent will be obtained from the child/adolescent in addition to parental consent. All consent forms describe that clinical, neurobehavioral and neuroimaging data will be stored at a central data management facility, as part of a national resource of data and materials distributed by NIMH for genetic analysis; provide assurance that such data will be provided to a central facility without personal identifiers; disclose that analyses of these data will also be conducted by other scientists currently not included within the current research team; and disclose that there is no plan to provide subjects with any financial benefits from any potential commercial products derived from the data. Research staff will review the informed consent document section by section with each prospective participant. This process will be done in the presence of a witness, often another family member, research staff person, or clinician. Participants will be given the option of reading through the document himself/herself, or having it read to him/her, as an initial step toward explanation of what participation entails. Participants’ questions will be answered throughout. The research staff person will take care to explain fully the following issues: the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, and the steps to be taken to protect confidentiality of information. Potential physical risks, and risks involving breach of confidentiality will be emphasized. The research staff person will confirm the participants correct understanding of each of these issues through appropriate questioning of the participant. If there is reason to suspect that a persons mental state is impaired enough to cast doubt on their ability to provide informed consent, the research staff will not proceed and will not include them in the study.

**Children and Adolescents**

For participants ages 11-17, assent will be obtained from the child/adolescent in addition to parental consent.

**Adult Subjects Not Competent to Give Consent**

All adult subjects will be competent to give consent. The research staff person will confirm the participants correct understanding of all aspects of the research through appropriate questioning of the participant. If there is reason to suspect that a persons mental state is impaired enough to cast doubt on their ability to provide informed consent, the research staff will not proceed and will not include them in the study.

**Potential risks**

Known risks from participation in this study are minimal.

*For all studies:* Fatigue, anxiety and discomfort are potential adverse effects associated with the tasks, symptom assessments, or other aspects of the study, but not more so than encountered during the performance of routine physical examinations or tests. Subjects (if 18 years old or older) will be asked about past traumatic experiences that they may have had. These questions may cause discomfort for individuals. Subjects will be informed that they can refuse to answer any question that makes them uncomfortable. Subjects will also be made well aware that they can continue participation in the study even if they refuse to answer certain questions. Minors (if under 18) will not be asked these questions about past traumatic experiences. We will attempt to minimize them by familiarizing participants with the personnel, setting and closely monitoring them during the study, and debriefing them at the end of the study. The study is conducted by investigators and staff with extensive experience and expertise who are sensitive to the clinical state of participating individuals.

*For reward studies:* Because there is a theoretical risk that for subjects with a history of problem gambling, the monetary reward task could cause distress or trigger gambling behavior, subjects with any history suggesting problem gambling will be excluded. Otherwise, participation in the study is not expected to cause any form of physical, psychological, social, economic or legal risks. All subjects will be briefed regarding the details and purpose of the experiment and will have the opportunity to have any questions answered prior to testing. The experimenter will also answer any question that the subjects may have.

*For fMRI studies:* The known risks associated with the fMRI studies are minimal. The levels of energy used to make magnetic resonance measurements are far less than are used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques.  The radio waves and magnetic fields, at the strengths used, are felt to be without harm.  This study may include the use of custom manufactured head coils and experimental imaging sequences that are not FDA-approved but are considered non-significant risks.  Because the magnetic field of the fMRI scanner attracts metal, the greatest risk is a metallic object flying through the air toward the magnet and hitting the participant. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal or magnetic objects are allowed in the magnet room at any time. Participants will be asked to place all metallic and magnetic objects in their possession (e.g. keys, jewelry, credit cards) in a locker outside the magnet room. In addition, once the participant is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room. Individuals will not be permitted to participate in the study if they have electrically, magnetically or mechanically activated implants such as cardiac pacemakers, clips on blood vessels in their brain, or other metallic objects in their body such as permanent retainers, orthopedic pins or plates, shrapnel, bullets, buckshot, or metal fragments. A checklist will be given to the participant before entering the MRI room, which will be reviewed and used to verify that they do not have any non-removable metallic objects or implanted devices in their body prior to participation. Most people do not find an MRI scan uncomfortable. However, on occasion some subjects have reported mild discomfort. The following are some types of discomfort that have been reported. The MRI machine is noisy, because of the knocking and beeping sounds that resonate when the magnetic gradients are pulsed. All participants will be given disposable earplugs or padded headphones to reduce the noise. Also, some people have reported feeling claustrophobic in the MRI machine. Participants will be made aware of this possibility, and we will ask individuals to refrain from participating if they tend to experience feelings of claustrophobia. If subjects become uncomfortable inside the magnet, they may withdraw immediately from the study. During some of the MRI scans, some subjects have reported temporary dizziness upon being moved into the field. This dizziness lasts less than 10 minutes. Also, some people have reported a metallic taste in their mouth, which can be associated with fillings in their teeth. Finally, due to the rapid rate of change of the magnetic gradients during imaging, the possibility exists for peripheral nerve stimulation. If this happens, subjects may feel a tingling or twitching sensation, typically along their arms or legs. This sensation is temporary, and stops when the scan ends. Participants will be instructed to notify the research staff if, at any time, they feel uncomfortable, no matter what the reason. Participants will be in contact with the research staff throughout the study through a microphone mounted on the MRI scanner. Participants will also be instructed in how to use an emergency handheld device to inform the operator if they wish to immediately stop scanning and be removed from the magnet. Scanning can be stopped at any time at their request. Participants will be informed that they should contact the PI if they have experienced a research-related injury. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since pregnant women receive no direct benefit from participating, we will exclude pregnant women from this study. A negative urine pregnancy test will be mandated before a woman of childbearing potential can participate in the imaging segment of this study.

**Potential benefits**

This is not a treatment study, and we do not anticipate the study will provide any direct benefits to participants.

We anticipate that the novel results produced by this research program may be useful in deploying targeted early interventions for irritable youths in order to achieve better and more durable outcomes. In future clinical trials, irritable youths may be stratified based on brain imaging phenotypes to predict response to both psychological (e.g., cognitive behavior therapy) and pharmacological interventions. Participants may obtain some gratification in participating in research they consider of value to others. The minimal risks to subjects are reasonable in relation to the anticipated benefits to others.

**Data and Safety Monitoring**

Data and safety monitoring will be conducted by the PI with assistance from the study team, whose members will be fully trained in necessary protocols, procedures and regulatory guidelines. Routine procedures are in place at the Schizophrenia Research Center (SRC) to ensure the safety, confidentiality, and integrity of subjects and data on an ongoing basis. In addition, the PIs and study team will perform a full monitoring review (including source data verification and review of all regulatory documents) on a yearly basis. As described above under Statistical Methods, the SRC has a Data Core that performs subject tracking, database management, data entry, data validation, quality assurance, and data verification on an ongoing basis to ensure validity and integrity. Subject privacy and confidentiality is rigorously maintained in accordance with HIPAA regulations, using secure databases that separate study data (linked to unique research identifiers) from any information that could reveal the subjects’ identities. Informed consent is obtained from all participants. The study may be terminated at any point, at the subject’s request or upon the judgment of the PIs or study team. If, in the clinical judgment of the PI, or the study team, the participant is found to meet any of the exclusionary criteria, or if the patient shows any potential medical complication at the time of the study, the study will be terminated. In the case of premature termination from the study, the subject will be informed of the need to terminate. In addition, depending on the nature of the problem, permission will be sought from the subject to convey any relevant information to the primary physician, so that it can be used to further the care of the patient.

**Risk/Benefit**

The physical, psychological, social, legal, or any other risks to participants involved in this study are minimal. Behavioral testing and MRI scanning procedures have been administered to many different patient populations and healthy volunteers in both clinical settings and research laboratories. They are standard, well recognized procedures that entail minimal risk to the subject. The personnel participating in these studies are well experienced in the administration of these procedures. It will be emphasized that the participant is free to withdraw from participation at any point. There is no direct benefit to subjects from their participation, aside from the monetary compensation for their time and travel. This study will contribute knowledge regarding the complexities inherent in irritability. This provides benefit to society, as well as potentially being of future benefit to patients and their families.