**Application for Review of Human Research:**

**IRB Protocol Summary-- Biomedical Research**

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Version: #6

**PROTOCOL TITLE**

***1. Full Title***

**Longitudinal Mapping of Network Development Underlying Executive Functioning in Adolescence**

 ***2. Brief Title***

**Imaging of Executive Function in Youth**

**STUDY SPONSORSHIP**

***1. Funding Sponsor***

NIMH R01MH113550

***2. Primary Sponsor***

Theodore D. Satterthwaite, MD, MA

**500 WORD PROTOCOL ABSTRACT**

Executive function (EF) undergoes dramatic development during adolescence, and is impaired across multiple psychiatric disorders such as ADHD and psychosis. Despite this fact, the neural substrates of EF development remain incompletely understood. Here, we propose to study the development of EF using cutting-edge techniques from network science. In this proposal, we will recruit 180 participants ages 8-18. This sample will include 65 with ADHD, 65 with psychosis-spectrum diagnoses, and 50 typically developing comparators. Using an accelerated longitudinal design, all participants will be followed and undergo cognitive testing, clinical assessment, and advanced multi-modal neuroimaging at 18 month intervals, yielding an average of 2.5 sessions per participant. This design will allow us to chart the development of structural and functional brain networks during adolescence, and delineate how abnormalities of brain network development are associated with deficits in EF performance, activation, and dynamics. Our overarching hypothesis is that the development of modular yet integrated brain networks during adolescence allows for specific patterns of EF activation and dynamics, and represents a fundamental mechanism for EF development. We posit that abnormalities of network development will be associated with executive dysfunction that is dimensionally present across psychiatric disorders such as ADHD and psychosis. This proposal capitalizes on complementary skills of the PIs and the research team, including expertise in brain development, network science, psychopathology, cognitive science, and high dimensional imaging statistics. Through the proposed multi-level analysis, this innovative research will provide a substantial advance in our understanding of the neurodevelopmental substrates of executive dysfunction across psychiatric disorders in adolescence.

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Executive function (EF) undergoes dramatic development during adolescence, and is impaired across multiple psychiatric disorders such as ADHD and psychosis. Despite this fact, the neural substrates of EF development remain incompletely understood. Here, we propose to study the development of EF using cutting-edge techniques from network science. In this proposal, we will recruit 180 participants ages 8-18. This sample will include 65 with ADHD, 65 with psychosis-spectrum diagnoses, and 50 typically developing comparators. Using an accelerated longitudinal design, all participants will be followed and undergo cognitive testing, clinical assessment, and advanced multi-modal neuroimaging at 18 month intervals, yielding an average of 2.5 sessions per participant. This design will allow us to chart the development of structural and functional brain networks during adolescence, and delineate how abnormalities of brain network development are associated with deficits in EF performance, activation, and dynamics. Our overarching hypothesis is that the development of modular yet integrated brain networks during adolescence allows for specific patterns of EF activation and dynamics, and represents a fundamental mechanism for EF development. We posit that abnormalities of network development will be associated with executive dysfunction that is dimensionally present across psychiatric disorders such as ADHD and psychosis. This proposal capitalizes on complementary skills of the PIs and the research team, including expertise in brain development, network science, psychopathology, cognitive science, and high dimensional imaging statistics. Through the proposed multi-level analysis, this innovative research will provide a substantial advance in our understanding of the neurodevelopmental substrates of executive dysfunction across psychiatric disorders in adolescence.

**OBJECTIVES**

**1. Overall Objectives**

**Aim 1: To delineate the longitudinal maturation of brain networks associated with executive dysfunction in ADHD and PS.**

*Hypothesis 1:* Modular, integrated structural and functional brain networks will emerge longitudinally with development. Impaired development of modularity quality and global efficiency will be correlated with common EF deficits across ADHD and PS. We will also test for divergent mechanisms of executive dysfunction across disorders; however, we expect common circuit-level deficits will be more robust.

Similarly, we expect development of modular and integrated topology to be specifically related to EF, with weaker or non-significant associations with other cognitive domains.

**Aim 2: To describe how abnormalities of functional activation and dynamics are related to EF deficits in ADHD and PS.**

*Hypothesis 2:* Executive system activation and temporal flexibility will increase with development and associate with EF. Structural equation models will reveal that patterns of activation and dynamics are facilitated by modular, integrated network topology and mediate the observed improvement of EF with age. EF deficits seen in both ADHD and PS will accordingly be associated with reduced activation of fronto-parietal executive regions, impaired de-activation of the DMN, and reduced dynamic flexibility.

**Aim 3: To integrate high-dimensional imaging data and define a multivariate predictor of executive dysfunction.**

*Hypothesis 3:* Machine learning models using longitudinal change in multi-modal imaging data will accurately predict single-subject EF at the final time point.

**Aim 4**: **To create a public resource to accelerate research on developmental deficits in EF.**

Publically available datasets are a critical catalyst to advances in science. However, accessible datasets including longitudinal neuroimaging in adolescents with psychopathology are rare. In **Aim 4** of this proposal we propose to share both raw and processed data, in tandem with all software used for data processing and analysis. Sharing processed data removes barriers to using public data, as it obviates the time-consuming processing and quality-assurance steps, which require substantial computational infrastructure. Well-documented processing pipelines and analytic software allows for *reproducibility* of processed data and *replication* of published results. We expect that this dataset will attract considerable interest from diverse classes of investigators in psychiatry, biomedical imaging, neuroscience, and developmental psychology.

**Primary Outcome Variables**

1. Executive summary score from factor analysis of cognitive testing
2. Segregation of functional and structural networks (modularity quality)
3. Activation during the working memory task (2-back versus 0-back)

**Secondary Outcome Variables**

Secondary outcome variables will consist of regional measures of brain structure and function.

**Background**

Executive function (EF) undergoes a protracted period of development throughout adolescence and young adulthood. Executive deficits negatively impact everyday function, and contribute to diminished quality of life in many clinical populations including ADHD and psychosis. Consequences of executive deficits may be particularly acute in adolescence, and include increased interpersonal conflict, decreased academic achievement, and risk-taking behavior. EF encompasses multiple cognitive components including working memory, inhibition, set shifting, sustained attention, and interference control. In contrast to other cognitive functions that may be more localized, most complex executive tasks have been shown to rely upon a spatially distributed network of brain regions, including the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), frontopolar cortex, anterior insula, superior parietal cortex, and thalamus.

Previous case-control studies have provided ample evidence of EF impairment across a wide range of psychiatric disorders including attention deficit hyperactivity disorder (ADHD) and disorders on the psychosis-spectrum (PS), such as schizophrenia. Preliminary data demonstrates that executive deficits in PS youth are similar in magnitude to those observed in ADHD. Furthermore, beyond such similar behavioral deficits, our recent work suggests a common neural mechanism for EF deficits across disorders. Rather than being associated with a specific clinical presentation such as ADHD or PS, impaired activation of frontal, parietal, and thalamic regions during a working memory task scaled with EF deficits across disorders. These results emphasize the significance of EF as a critical dimension of brain function that cuts across clinical diagnostic categories including ADHD and PS. Thus, substantial data from both case-control studies and our preliminary work support the scientific premise of this research.

Despite clear clinical relevance, the developmental mechanisms of EF maturation and dysfunction in adolescence remain incompletely described. Because of the spatially distributed nature of EF, typical regionally-focused analyses lack explanatory power. Accordingly, we propose to delineate the developmental substrates of EF using tools from network science. Regions critical for EF fall within several large-scale functional networks, including the fronto-parietal control network, the cingulo-opercular network, and the salience network.

Additionally, existing work from our group has demonstrated that accurate performance on a challenging EF task is associated with reciprocal de-activation of non-executive regions within the default mode network (DMN) such as the posterior cingulate (PCC) and ventromedial prefrontal cortex (vmPFC). Furthermore, preliminary data indicates that the functional dynamics of EF evolve to become more flexible with age, with more frequent transitions between such activation states. These results accord with our recent work in adults, where we have shown that network flexibility is associated with EF performance. Thus, extensive data further support our premise that EF can be conceptualized as a complex network process that relies on flexible patterns of activation among specific executive networks and suppression of DMN regions.

Modularity is a fundamental feature of complex systems, including social groups, cyber-physical systems, and diverse biological networks. Human neuroimaging studies have demonstrated that the human brain has a well-defined modular organization, as reflected in the presence of large-scale functional networks. A remarkable convergence exists across independent datasets and laboratories in number and spatial locations of functional network modules. Prior research and our own preliminary data suggest that during adolescence both structural and functional brain networks become increasingly modular, with segregation among functional sub-systems. However, alongside such increased modularity, we have recently found that brain networks simultaneously become integrated through targeted strengthening of specific hub connections that provide links across the boundaries between modules (see grant). We propose that this pattern of network development allows for both functional specialization within as well as coordination among the many regions EF relies upon, and may constitute a fundamental developmental mechanism for the emergence of EF in adolescence. Indeed, preliminary data indicate that both network modularity and network integration are associated with and mediate the development of executive performance.

While these preliminary data provide strong support for our model, limitations of existing data underscore the outstanding gaps in our knowledge that motivate the current proposal. First and foremost, all preliminary analyses used cross-sectional data, which have well-documented limitations for inference regarding developmental trends, and preclude analysis of within-individual change over time. Second, our existing data are drawn from a community-based sample, and it is not clear whether these mechanisms generalize to clinically-ascertained youth with ADHD or PS. Third, it remains unknown how the longitudinal development of network topology is associated with emergent patterns of activation and dynamics, and whether integrating such multi-scale data could yield longitudinally predictive biomarkers of EF deficits in clinical populations.

**Study Design**

**Phase**Not Applicable.

**Design**

This is a longitudinal study that will follow participants over the course of five years, who will be evaluated and imaged between 2 and 3 times throughout their participation in the study. Participants will be recruited using screening mechanisms provided by LiBI (CHOP IRB #16-013305), a research institute that spans both CHOP and Penn. Through LiBI, large numbers of children and adolescents in both child psychiatry and general pediatric clinics are screened for research studies, ensuring that participant accrual will be highly feasible. Patients (n=126 total) will be drawn from two clinical groups with well-documented executive deficits: ADHD and PS (n=63 per group). Both patient groups and typically-developing comparators (n=49) will be matched on age, sex, and race.

All participants will be assessed and imaged twice, however, participants who enroll in the first half of the project period will be able to complete a third session. Thus, participants will be assessed and scanned 2 to 3 times over 5 years in order to observe executive function during a critical period of ongoing brain development (childhood and adolescence). Participants will be assessed using a detailed diagnostic interview and computerized neurocognitive battery, identical to the ones used by protocol #813943 and LiBI, and self-report scales. We will use longitudinal change in imaging data to predict EF across groups. The Diagnostic Interview and Computerized Neurocognitive Battery will be done through the LiBI protocol (CHOP IRB #16-013305) and participants will thus sign the consent forms associated with these protocols (see attached for review). We will be collecting consent and administering a portion of study procedures electronically, over the phone, or using BlueJeans or similar HIPAA-compliant, IRB and University approved teleconferencing systems.

If participants have received a clinical assessment via another lab protocol (e.g., IRB #813943, CHOP IRB #16-013305) within 1 month of their imaging visit, we may not repeat the clinical assessment and we will only have them come in for the imaging visit at that time point. 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 database to recruit these individuals for a new study. Coordinators receive database access only through PI approval and after completed training with the data core. As described in the Neuropsychiatry Section’s center-wide protocol (#813943), and LiBI’s protocol (CHOP IRB #16-013305), 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.

**Study Duration**

This is projected to be a 5-year study, with start date contingent upon IRB approval and an end date of July 1, 2023.

**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 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**

In this proposal, we will address these limitations and conduct longitudinal imaging in a sample of 180 adolescents (ages 8-15 at study entry, age 18 by study completion), including 65 with ADHD and 65 with PS, as well as 50 typically-developing comparators.

**Subjects at Penn**

180

**Subjects at Sites other than Penn**

0

**Accrual**

Participants will be recruited using screening mechanisms provided by LiBI, a research institute that spans both CHOP and Penn. Through LiBI, large numbers of children and adolescents in both child psychiatry and general pediatric clinics are screened for research studies, ensuring that participant accrual will be highly feasible. Consistent with the RDoC approach, patients (n=130 total) will be drawn from two clinical groups with well-documented executive deficits: ADHD and PS (n=65 each). Both patient groups and typically-developing comparators (n=50) will be matched on age, sex, and race. All participants will be assessed and imaged twice, while participants who enroll in the first half of the project period will be able to complete a third session. In order to maximize retention and foster study engagement, participants will be contacted every four months by phone, receive study updates via an e-news letter sponsored by LiBI, and be invited to events at LiBI. LiBI’s consent/assent forms and protocol are attached in this submission for IRB review.

The Neuropsychiatry Section utilizes a common, center-wide protocol (IRB #813943). Participants may also be drawn from a large pool of subjects who have agreed to be contacted for research as part of this protocol #813943. This protocol provides the Neuropsychiatry Program with common procedures including recruitment, screening, mobile phenotyping, and clinical assessment. Please refer to this protocol for a complete description of all subject accrual procedures.

As participants from both recruitment pools were originally recruited from CHOP, potential participants may undergo additional screening via CHOP medical record review prior to recruitment. CHOP medical record review may also be used to obtain updated contact information when available.

**Key inclusion criteria**

All subjects:

Age 8-15 years at enrollment, and age 18 or less at final follow-up visit. The relatively broad enrollment age range is required to allow even sampling of the entire age range of interest (8-18) during the 5-year project period in this accelerated longitudinal design.

Patients (n=130):

Each participant will meet diagnostic criteria for either ADHD or PS (see Assessment, below). Given known and substantial co-morbidity between PS and ADHD (i.e., approx. 30% in the PNC), co-morbidity will be allowed and accounted for in specificity analyses. Youth meeting criteria for both PS and ADHD will be considered PS for enrollment purposes.

Typically developing (n=50):

No current or lifetime history of any DSM-V diagnosis or substance use disorder.

**Key Exclusion Criteria**

All subjects:

1) Metallic implants, claustrophobia, or other contraindications to MRI

2) Significant medical or neurological illness that impacts brain function or impedes participation

3) Acute intoxication with alcohol or other substances based on clinical assessment or subject report.

4) Pregnancy. Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. As in accordance with current guidelines from CAMRIS, we will assess pregnancy by verbal attestation from participants that they are or are not pregnant.

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**

Because this study enrolls minors, the process for minor participants will include the child and their parental guardian(s). Participants and their guardian will meet with a trained Research Coordinator who will explain the research and its goals. After full explanation of all the research procedures and reading the assent/parental permission forms, informed consent will be obtained from the participant and their parental guardian; however, if there is reason to suspect that the participant’s mental state is impaired enough to cast doubt on the validity of the statement of consent, they will not participate. Research staff will review the informed consent document section by section with each prospective participant. 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**

Participants will be recruited using screening mechanisms provided by LiBI, a research institute that spans both CHOP and Penn or Penn’s center-wide common protocol (#813943).

**Subject Compensation**

As described in detail below, the study will be separated into two study visit days. The first visit will include a standard diagnostic interview and cognitive testing; the second visit will include neuroimaging and other clinical phenotyping procedures. Participants will complete study visits 1 and 2 up to 3 times over the 5-year period. A small percentage of subjects may have already received the standard diagnostic interview and cognitive testing under a separate protocol such as the Penn/CHOP LiBI protocol or Penn IRB #813943 and therefore will only receive the second study visit that includes neuroimaging and other clinical phenotyping. Payment for each day is outlined below and further descriptions of these procedures are outlined under the Procedures section:

Day 1: Psychiatric and Cognitive Assessment

At their first timepoint, 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 Penn/CHOP LiBI protocol and the center-wide protocol at the Neuropsychiatry Section. Subject compensation for the clinical assessment and the neurocognitive battery activities for this protocol will be as follows:

* $40 for the Clinical Evaluation/Assessment (2-4 hours)
* $40 for the Computerized Neurocognitive Battery (1 hour)
* Participants will also be reimbursed for travel expenses (transportation and parking)
* If a subject appears intoxicated at the time of the visit, 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 first imaging visit, participants will be paid a flat payment of $100. At the second and/or third time point(s), they will be compensated $150, broken down by type of procedure completed at once, because they may receive more extensive and detailed clinical and behavioral phenotyping therefore adding time and effort to the study visit. Furthermore, the second and/or third timepoint visits may be broken up over two days. At every study visit, participants will also be reimbursed for travel expenses. If participants complete all study visits, a completion bonus of $150 will be granted.

* Imaging Visit 1: flat payment $100 + travel expenses
* Imaging Visit 2 and/or 3: $60 (MRI) + $20 CNB (long) +$20 decision making tasks + $40 CNB (long) +$10 self-report questions + travel expenses
* Completion bonus (paid on final visit 2 or 3): $150

If a subject appears intoxicated at the time of the visit by 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).

These amounts are deemed to provide some compensation for time, travel and discomfort, without being coercive. The completion bonus ($150) is necessary to allow appropriate compensation for completed participation and reducing subject dropout, since interpretable results from this within-subject longitudinal design requires complete data from at least two visits.

We plan to implement 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. In order to be paid, participants must provide their 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 payment method during the phone screen.

For subjects paid via ClinCard, we will provide subjects with free replacement ClinCards if they happen to lose their card or if it is stolen. However, study staff will stress the importance of holding onto the card and storing it in a safe place to avoid losing it. If the Clincard is not used for any purchase or withdrawal within 6 months, a $4.50 fee will be incurred each month until the remaining balance is spent. Participants will be made well-aware of this fee during the consent process. 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.

**Procedures**

The study involves several segments, the procedures for which are addressed separately here. All participants will complete parts 2 and 3 during two separate time-points, while participants who enroll in the first half of the project period will be able to complete an additional third session (also comprised of parts 2 and 3 below).

1. Pre-Study Screening and Recruitment Procedures

Participants will be recruited using screening mechanisms provided by LiBI, a research institute that spans both CHOP and Penn’s Neuropsychiatry protocol #813943. Through LiBI, large numbers of children and adolescents in both child psychiatry and general pediatric clinics are screened for research studies, ensuring that participant accrual will be highly feasible. Consistent with the NIMH Research Domain Criteria (RDoC) approach, patients will be drawn from two clinical groups with well-documented executive deficits: ADHD and PS. Abbreviated pre-study screening procedures will be used for subjects who have already received clinical assessment and baseline neuroimaging as part of that protocol.

Following pre-screening 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

Assessment: All subjects will receive detailed assessments to comprehensively evaluate EF capacity in the context of psychiatric diagnosis and document functioning in other cognitive domains. Assessment of youths and collateral information from parents will take place in a single 3-5 hour visit that will be performed within 1 month of neuroimaging. Informed written consent will be obtained from the parent/guardian of the participant, and assent will be obtained from the participant. We will be collecting consent and administering a portion of study procedures electronically, over the phone, or using BlueJeans or similar HIPAA-compliant, IRB and University approved teleconferencing systems.

Assessment of EF: As the broad construct of EF is composed of specific sub-domains, we will assess EF using a battery of tasks that specifically probe components of EF (see Grant attached in HSERA).

Multi-domain assessment of cognition: Beyond measures of EF, all participants will complete the Penn CNB, which assesses a broad range of cognitive domains beyond EF, including episodic memory, complex reasoning, social cognition, and motor function. Specificity of relationships with EF will be evaluated in all aims. Reward-related decision-making will be assessed using a dedicated battery of tests as described below.

Clinical diagnostic assessment: All subjects will receive a detailed diagnostic assessment from highly-trained assessors using a computerized version of the K-SADS interview, which includes semi-structured assessments of ADHD, psychotic disorders, mood and anxiety disorders, and substance use disorders. As in our prior work, prodromal symptoms of psychosis will be assessed using Structured Interview for Prodromal Symptoms. Furthermore, the Scale of Prodromal Symptoms (SOPS) will be administered along with the SIPS; the SOPS rates the severity of prodromal, psychotic, and other symptoms occurring within the past 6 months.

To meet inclusion criteria in the PS group, participants must meet standard criteria for either a psychotic-spectrum disorder on the K-SADS or the Attenuated Prodromal Syndrome (APS) provided by the SIPS.

For all instruments, information will be provided by a collateral interview of a parent or guardian, and integrated to yield a consensus diagnosis at clinical case conference led by at least two doctoral-level clinicians. All clinical data are collected and stored in a secure RedCAP database.

3. Neuroimaging Protocol

The imaging visit lasts approximately 4-5 hours. All subjects will undergo longitudinal neuroimaging as part of this study. Images will be acquired in a one-hour session using a research-dedicated 3T Siemens Prisma Scanner. All sequences will be harmonized with the landmark Adolescent Brain Cognitive Development (ABCD) study, to facilitate data pooling and sharing. Sequences acquired will include T1 and T2 sequences to assess brain structure, diffusion imaging for structural tractography, and fMRI to measure EF activation, functional connectivity, and task-based functional dynamics. As in ABCD, intrinsic connectivity scanning will be broken into four brief (~5 min) runs to reduce in-scanner motion. Prior to scanning, a practice task may be conducted inside a mock scanner environment, which acclimatizes participants to the environment and minimizes novelty effects. During certain sequences, participants will watch a movie in order to help them lie as still as possible and stay awake. Research shows that showing movies during the MRI is effective in reducing participant motion, particularly in children and teenagers. Depending on the participant’s age and their parental guardian’s preference, participants will watch either a G-rated (e.g., Finding Nemo) or PG-rated movie (e.g., Harry Potter) during the scan. This is also standard protocol in the ABCD 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 and mood symptoms, 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 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.

Diffusion imaging: a ~10 minute diffusion imaging scan will be performed to measure white matter microstructure. This scan allows reconstruction of structural brain networks using probalistic tractography.

Functional Images: 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. Both task fMRI and resting-state sequences measuring functional connectivity in the absence of task conditions will be acquired. Specifically, all participants will complete a working memory fMRI task. We will probe EF in the scanner using a fractal version of the n-back working memory (WM) task. This has been used in many prior studies in our laboratory, including IRB #810336 and #822831.

Post-scan procedures: Subjects will rate their level of interest, effort, and emotional response to the tasks. Mood and anxiety will also be assessed after scanning.

In addition to scanning, participants may also complete self-report questionnaires and decision-making tasks, outlined below. We will be administering a portion these study procedures electronically, over the phone, or using BlueJeans or similar HIPAA-compliant, IRB and University approved teleconferencing systems.

*Additional symptom assessments:* Dimensional ADHD symptoms will be assessed using the Strengths and Weaknesses Scale, which has excellent psychometric properties, allowing for greater sensitivity to detecting dimensional relationships. Irritability will be assessed using the Affective Reactivity Index (ARI). Symptoms of depression will be measured using the mood and feelings questionnaire. Trait anxiety and anxiety at the time of scanning will be assessed using the State-Trait Anxiety Inventory. Other anxiety domains will be assessed using the Screen for Child Anxiety Related Emotional Disorders. All state-specific scales will be administered at the time of scanning.

Moreover, as in protocol #810211 and IRB #822831, these measures may include, but are not limited to, standard instruments such as: 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) or the PROMIS anxiety scale. The Fagerström Test for Nicotine Dependence (FTND) may be used to measure nicotine dependence severity. Gambling may 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), PROMIS depression, 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 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). We may also administer newer scales such as eSWAN scales ADHD, DMDD, Social Anxiety, Depression, and Panic Disorder. Other standard psychological scales may be administered as well.

*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 executive dysfunction. In particular, certain decision- making tasks that require restraint of affective systems through executive function are especially likely to be impaired in the context of executive dysfunction. 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. These tasks will target a wide range of cognitive functioning including memory, attention, processing speed, effort and motivation, risk-taking, and inhibition.

**Statistical analysis**

***Analytic methods pertinent to all aims.***

**Subject level image pre-processing**

The primary confounding artifact in developmental neuroimaging studies of brain networks is motion artifact, which is correlated with variables of interest including participant age and cognitive ability. Our group has led the field in describing the impact of this confound and devising strategies to reduce its influence, complementing work from other groups. All subject-level preprocessing described below utilizes proven techniques to mitigate motion artifact, and thus *reduce bias and enhance scientific rigor*.

Task fMRI**:** Subject-level time series analysis will utilize FSL. The contrast map of interest in the fractal *n*-back task used in Aim 2 is the 2-back vs. 0-back. Pre-processing will include volume-censoring, which markedly reduces the impact of motion artifact.

Resting-state fMRI*:* We developed a widely-used, pre-processing pipeline to minimize the influence of signal artifacts related to subject motion. This pipeline will be used in Aim 1 and includes high-dimensional confound regression as well as despiking and spike-regression of high-motion volumes.

Diffusion imaging: Eddy currents and distortion of diffusion images will be estimated and corrected using FSL’s `eddy` tool. Following calculation of fractional anisotropy (FA), probabilistic tractography will be used for Aim 1, applying tools included in FSL that allow for improved resolution of crossing fibers using multiple diffusion shells. Quality-assurance (QA) will be conducted using a dedicated pipeline optimized for adolescent studies.

**Longitudinal image registration procedures:** We will use an advanced, validated longitudinal processing approach that minimizes bias 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 and tissue priors 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 be performed using the top-performing deformable registration provided by ANTs. Co-registration of the other imaging modalities to the T1 image will utilize boundary-based registration. Each modality will be mapped smoothly to the custom template space using only one interpolation by concatenating all transforms.

**Group level analysis: general additive mixed models***.* In Aims 1 and 2, we will examine developmental effects and associations with EF using general additive mixed models (GAMMs). Brain development is not a linear process; use of penalized splines within a mixed-effects general additive model allows us to estimate both linear and nonlinear longitudinal brain development in a data-driven fashion. This approach allows flexible modeling of nonlinearities, but avoids over-fitting the data by applying a penalty for increasing levels of nonlinearity, which is estimated from the data using restricted maximum likelihood. GAMMs can be technically challenging to apply to high-dimensional neuroimaging data, but in collaboration with Co-I Shinohara we have recently created a software library for use in R to facilitate application of these complex models to imaging data (package `voxel` in CRAN: [https://cran.r-project.org/web/packages/voxel/index.html)](https://cran.r-project.org/web/packages/voxel/index.html%29). Based on recent evidence showing the deficiencies in typical cluster-correction based methods,81 all analyses in this proposal will use the False Discovery Rate (Q<0.05). *In accordance with NIH standards, all group level analyses will include sex as a biological variable of interest. Scientific rigor will be ensured by including confounding variables such as motion as model covariates.*

***Analytic approach for each specific aim***

**Aim 1**: **To delineate the longitudinal maturation of brain networks associated with executive dysfunction in ADHD and PS.**

*Hypothesis 1: Modular, integrated structural and functional brain networks will emerge longitudinally with development. Impaired development of modularity quality and global efficiency will be correlated with common EF deficits across ADHD and PS. We will also test for divergent mechanisms of executive dysfunction across disorders; however, we expect common circuit-level deficits will be more robust. Similarly, we expect development of modular and integrated topology to be specifically related to EF, with weaker or non-significant associations with other cognitive domains.*

The analytic approach proposed here uses cutting-edge methods from network theory that have been developed by PI Bassett. All methods have been extensively validated (and are published or under peer review) but have not yet been applied to study longitudinal brain development.

*Network construction.* Longitudinal structural and functional connectivity data will be used to construct brain networks after pre-processing as described above. Both structural and functional networks will use the recently-released 360-node multi-modal parcellation produced by the Human Connectome Project, facilitating integration across modalities. For each modality at each time point, this will yield a 360x360 symmetric adjacency matrix (comprised of 64,620 unique connections). For each subject, we will create a *multi-layer graph* composed of modalities (structure, function) and time points (2-3 per subject). We will define network modules for each subject in this multi-layer graph using a Louvain-like locally greedy community detection algorithm, applied 100 times to accurately sample the modularity landscape and identify a robust optimal partition of nodes into modules. We will use all 100 estimates to inform the final partition using consensus clustering, thereby reducing estimation bias and enhancing scientific rigor.

*Parameter selection, tuning, and null models*. The multilayer graph is constructed by placing identity links between node *i* and itself at consecutive time points (*temporal parameter*), and between node *i* and itself across both structural and functional brain graphs (*modality parameter*). The weights of these two types of identity links comprise two parameters in our model, and the third parameter tunes the size of detected modules (*resolution parameter*). We choose the parameter values using a data-driven approach that reveals the temporal and spatial resolutions at which salient modular network organization exists in the data, beyond that expected in an appropriate random network null model. Specifically, we perform a 3-dimensional parameter sweep and identify the point in that space that maximizes the consistency of partitions across iterative optimizations, and that also maximizes the differences between observed modularity and that present in the null model. While several multilayer null models have been applied to neuroimaging data, we will use the most stringent null relevant to our hypotheses regarding regional effects, which permutes the identity of brain areas uniformly at random to ensure a non-parametric assessment of statistical significance. *This null model comparison enhances the scientific rigor of our approach*.

*Measure of network modularity*. Detection of multi-layer community structure yields a multi-modal network partition for each participant, as well as an estimate of the modularity quality index (*Q*). This statistic will function as the summary index of network modularity; higher values of normalized *Q* indicate greater separation of brain regions into modules. As each individual’s multi-layer network partition is expected to vary, we will also derive a consistent across-subject partition using an iterative consensus clustering procedure. In the consensus partition, the quality of each module (*Qmod*)will be calculated both within and across modalities; use of a consensus partition for analysis of individual network modules will ensure across-subject correspondence of modules. For regional analyses, we will calculate the participation coefficient (*PC*), which measures the balance of within- *vs.* between-network connectivity.

*Measures of network integration*. In addition to these measures of network modularity, we will quantify network integration using *global network efficiency* (*Eglob* ): the harmonic mean of the inverse of the shortest path length between node pairs.90 We will use a recently developed extension of this metric for use in multi-layer graphs.

*Hypothesis testing:* This procedure yields multi-modal network segregation (*Q*) and integration (*Eglob*) for each subject at each time point. Changes with development and associations with EF deficits across ADHD and PS will be tested using GAMMs as above. For higher-resolution analyses of module-specific (*Qmod*)and regional segregation (*PC)*, we will apply an FDR (Q<0.05) correction for multiple comparisons. Mass-univariate connectivity analyses will complement such network measures.

Notably, our primary hypothesis is that that this modular, integrated network topology is primarily related to EF deficits across all participants. To ensure that group differences do not drive any observed dimensional results, group will be included as a covariate in this model (along with sex, in-scanner motion, and a non-linear spline term for age). However, we will also evaluate the alternative hypothesis that EF deficits are disorder-specific, by examining this association within each group separately, and by testing interaction analyses with group. We expect the across-group individual differences in EF to be most strongly linked to network topology.

Furthermore, we will evaluate the specificity of observed associations with EF by also examining other cognitive domains tested by the Penn CNB including memory, motor function, and social cognition. Based on both preliminary data (see below) and the distributed nature of executive networks, we expect network topology to be specifically linked to EF deficits in ADHD and PS.

**Aim 2**: **To describe how abnormalities of functional activation and dynamics are related to EF deficits in ADHD and PS.**

*Hypothesis 2: Executive system activation and temporal flexibility will increase with development and associate with EF. Structural equation models will reveal that patterns of activation and dynamics are facilitated by modular, integrated network topology and mediate the observed improvement of EF with age. EF deficits seen in both ADHD and PS will accordingly be associated with reduced activation of fronto-parietal executive regions, impaired de-activation of the DMN, and reduced dynamic flexibility.*

*Task fMRI:* All participants will complete the fractal *n-*back task at each visit; activation on the 2-back vs. 0-back condition will be related to EF performance using voxelwise GAMMs. We expect that activation in the executive system and de-activation of non-executive regions within the DMN will increase with age. Furthermore, we expect that this pattern of reciprocal executive activation and DMN de-activation will associate with individual differences in EF while controlling for age. Finally, we expect this age-related change in activation patterns will mediate any longitudinal improvement of EF performance.

*Functional dynamics*: Importantly, neither traditional task-based fMRI analyses nor studies of functional connectivity are able to assess changes in the patterns of dynamic activity in a time series. A novel method for assessing the flexibility of temporal activation patterns builds on an alternative application of network science tools to neuroimaging data. In particular, we begin by defining a brain state as a complex, multivariate pattern of regional activity at a single time point. Then, we can algorithmically collect time points with similar activity patterns using a graph-based clustering technique, identifying dominant brain states. Finally, we can study the temporal patterns by which the brain transitions from one state to another, estimating the rate of switching between states. This approach is closely related to techniques being concurrently developed in the graph signal processing literature,85 and allows us to ask how activation dynamics in the brain change over development and vary by EF capability.

*Hypothesis testing:* First, we will evaluate associations between EF deficits and measures of activation (2-back vs. 0-back contrast) and dynamic flexibility during the WM task. Our primary hypothesis is that EF deficits across all participants will be associated with impaired activation of executive networks (and reciprocal de-activation of the DMN) as well as reduced dynamic flexibility. The same model covariates will be used as for Aim 1, and identical specificity analyses will be conducted (i.e., categorical group differences, interaction analyses with group, and associations with cognitive domains other than EF).

*Structural equation models*:  Second, we will seek to link the findings of Aim 1 and Aim 2 using structural equation models. We anticipate that the longitudinal network reconfiguration described in Aim 1 allows for the emergence of patterns of activation and dynamics that are associated with accurate EF performance. To test these intermodal longitudinal relationships, the linear and nonlinear developmental change of the summary measures will be modeled using latent growth curve modeling, a special application of structural equation modeling. These models will allow us to test whether the relationship between EF performance change and network development is mediated by changes in task-related activation and dynamic flexibility. Structural and functional networks will be summarized for each subject, at each time point, by the network modularity (*Q*) and efficiency (*Eglob*)as described above.  Activation will be summarized as mean activation within the executive network (defined *a priori*from PNC data), whereas flexibility will be measured using the dynamic analysis described above.  Significance tests will use bootstrapped confidence intervals.

**Aim 3**: **To integrate high-dimensional imaging data and define a multivariate predictor of executive dysfunction.**

*Hypothesis 3: Machine learning models using longitudinal change in multi-modal imaging data will accurately predict single-subject EF at the final time point.*

Proposed approach: In this aim, we proposed to use multivariate pattern analysis (MVPA) techniques to integrate multi-modal neuroimaging data and predictdimensional EF function. By considering complex patterns in the high-dimensional data, such techniques have the potential to provide more sensitive and specific measures than standard mass-univariate methods. We propose to use state-of-the-art *generative-discriminative models,* which have notable advantages over standard machine learning methods. Critically, generative-discriminative models retain high predictive accuracy while yielding feature weights that are more interpretable, in this case because highly predictive sub-networks are required to form connected subgraphs. Generative-discriminative models predicting dimensionally defined EF at the final assessment session (i.e., time point 2 or 3) will be constructed in each modality separately and also across all modalities. In line with prior work in longitudinal studies of aging, model input data will reflect the rate of change of imaging features. Using longitudinal data facilitates predictive analyses by better accounting for between-subject variability and focusing on abnormalities in developmental rates of change that are likely to be discriminative.

*Model covariates and cross-validation:* One potential concern for such multivariate models is the influence of confounding covariates. At present, while standard practice in the field is to “regress out” confounders from imaging data, recent work by co-investigator Dr. Shinohara has demonstrated that such an approach can cause significant bias. This bias can be addressed by adapting techniques from the field of causal inference, allowing potential confounders such as age, sex, medication status, and data quality to be jointly modeled as a propensity score within the multivariate model. Applications of this technique to studies of aging have shown enhanced sensitivity to detect real effects and reduced influence of confounding covariates. As multivariate methods are flexible and risk over-fitting data, all analyses will be conducted using 10-fold cross-validation with separate training and testing samples. Validation folds will be stratified by group, age, and EF performance to ensure correspondence. Model and feature significance will be evaluated using permutation testing. *Together, attention to confounds and over-fitting ensures* *scientific rigor*.

*Hypothesis testing:* We will use longitudinal change in imaging data to predict EF across groups, controlling for covariates using propensity scores. Predictions using multi-modal imaging data will be compared to those using lower-dimensional clinical assessment data; as in prior work, we expect that prediction using imaging data will provide additional predictive accuracy over and above that provided by clinical data alone. We will also build separate models for ADHD and PS groups. Reflecting our hypothesis that EF deficits have common network-level deficits across groups, we expect that models trained on one group will significantly predict EF deficits in the other group. We expect that longitudinal change will be a more robust predictor of EF deficits than a simple cross-sectional value. However, we will explicitly test this hypothesis and compare the predictive accuracy of longitudinal data to that derived from cross-sectional data from the baseline session.

**Subject Confidentiality**

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

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

[x]  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.

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

[x]  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 participants 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 during the CNB 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.

Data for this protocol are to be collected and managed using REDCap and Oracle electronic data capture tools hosted at Brain Behavior Laboratory, University of Pennsylvania. These databases run on a secured Mac Server. The drive is encrypted and the system is housed in a secured room with controlled and monitored access on the University of Pennsylvania Health System Campus. The server is connected to a public network (PennNet) and protected by a built-in software firewall (IPFW). All unnecessary services are disabled. Access to the server is strictly controlled with unique usernames and passwords. Access to the databases are secured using unique usernames and passwords. All study personnel must receive PI approval for access to the databases.

**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 8-17, 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 archive maintained by NIMH. Data will provided to this facility without personal identifiers. Furthermore, the consent states that de-identified data may be shared with other scientists currently not included within the current research team and to the general public. Notably, participants and parents are informed that while they can choose to withdraw their data from the study, data that has already been shared cannot be deleted or retracted. Participants will not be compensated from any commercial products developed using openly shared study 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 person’s 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 8-17, 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.

**Electronic Consent**

We will also be collecting consent and administering a subset of study procedures electronically, over the phone, or using BlueJeans or similar HIPAA-compliant, IRB and University approved teleconferencing systems. Following consent, participants will be instructed to print or save the page for their records. This page will not include protected health information.

**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. 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.

**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 youths with executive function deficits in order to achieve better and more durable outcomes. In future clinical trials, youths with executive function deficits 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 executive function. This provides benefit to society, as well as potentially being of future benefit to patients and their families.