A. SPECIFIC AIMS

The overarching aim of this proposal is to examine competing neurobiological models of ADHD\textsuperscript{7, 8}. One of the best studied models suggests that children with ADHD suffer primarily from deficits in inhibitory control with impulsivity stemming from a failure to suppress urges\textsuperscript{9, 10}. A competing model, however, maintains that ADHD youth may also demonstrate hyperactivity due to abnormal emotional reactivity\textsuperscript{7, 11, 12}. Most neuroimaging studies have focused on the neural circuitry associated with either one or the other of these two neuropsychological domains\textsuperscript{12-14}. The critical hypothesis, however, is that deficits in both domains and functional abnormalities in both neural circuit can be associated with ADHD and determine the clinical phenotype that a particular child exhibits. This hypothesis is best examined by investigating simultaneously the functioning of both neural circuits in the same group of children as this is the best means to determine whether these two circuits have dissociable functions and neuropsychological correlates in children with ADHD. With this in mind, the specific aims and hypotheses for this 5-year project are the following:

**Aim 1:** To use functional magnetic resonance imaging (fMRI) to measure brain activity associated with inhibitory control during the performance of the Simon Spatial Incompatibility Task. The study will compare brain activity in children (ages 8-12) with ADHD (N=30) with that of age-matched control participants (N=30) performing the same task. **Hypothesis 1:** Compared with healthy children, children with ADHD will have reduced task related activations in the frontostriatal (FS) circuits that subserve inhibitory control.

**Aim 2:** To use fMRI to measure brain activity associated with self-rated emotional experiences generated in response to the viewing of emotion-denoting words during the performance of the Affective Circumplex Task. **Hypothesis 2:** Compared with healthy children, those with ADHD will have neural activity in the frontolimbic (FL) circuits that is a) progressively more exaggerated in association with increasing self-reported positive or negative valence, and also b) progressively more exaggerated in association with increasing self-reported arousal.

**Aim 3:** To examine associations of activity in FS and FL circuits with measures of cognitive and emotional functioning and symptom severity in children with ADHD. **Hypotheses (3A)** A double dissociation will be found in the behavioral correlates of FS and FL circuits during the performance of the above fMRI tasks such that: 1) task-related activations in FS circuits will correlate with behavioral measures of inhibitory control but not with measures of emotional reactivity, and 2) task-related activations in FL circuits will correlate with behavioral measures of emotional reactivity but not with measures of inhibitory control. **(3B)** Activity in FS circuits will mediate the relationship of an ADHD diagnosis with behavioral measures of inhibitory control. Conversely, activity in FL circuits will mediate the relationship of an ADHD diagnosis with behavioral measures of emotional reactivity. **(3C)** FMRI measures of activity in FS and FL circuits will have a cumulative influence on ADHD symptom severity.
B. BACKGROUND AND SIGNIFICANCE

B1. Frontostriatal Circuitry and Inhibitory Control: A Neurobiological Model of ADHD

Inhibitory control denotes the capacity to suppress a prepotent response in favor of a more suitable one. Barkley and others suggest that an impaired capacity to inhibit responses is the core deficit in ADHD and leads to secondary impairments in a broad range of executive functions (i.e., goal-directed thoughts and behaviors). This claim is based on the supposition that virtually all executive functions require some type of inhibitory control. Competing urges and distractions are omnipresent and must routinely be inhibited or suppressed long enough for executive functions to be completed. Therefore, when inhibitory control is impaired, other executive functions suffer as well. Translating these impairments into neurobiological terms has been a major area of investigation and has lead many researchers to suggest that children with ADHD have functional and structural abnormalities within frontostriatal circuits, a neural network thought to support cognitive control, working memory, set-shifting, and inhibitory control. (see Figure 1)

![Figure 1](image_url)

This FS/ inhibitory control model of ADHD has substantial empirical support but also significant shortcomings. Findings across studies of children with ADHD have been inconsistent both in terms of behavioral and neuroimaging data. For example, the FS/inhibitory control model of ADHD predicts that deficits in inhibitory control should be virtually universal in ADHD children and yet only 35-50% of youths with ADHD demonstrate deficits in this, or any related, domain. Likewise, deficits on other neuropsychological measures of executive function similarly capture only a limited portion of children with the disorder. Moreover, whereas neuroimaging studies of FS circuits suggest volumetric and functional abnormalities in dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (ACC), dorsal caudate, and putamen, findings have been inconsistent both in terms of volumetric differences and functional activations. Taken together, extant behavioral and neuroimaging studies of pediatric ADHD suggest that the FS/ inhibitory control model of ADHD is an important framework for beginning to understand the neurobiology of ADHD, but that it cannot capture the full complexity or heterogeneity of this syndrome.

Figure 1 Schematic representation of symptom formation and associated neural circuitry in the FS model of ADHD

1A. In this model of ADHD, symptoms are thought to be a consequence of impaired inhibitory control with secondary deficits in other executive functions. 1B. The underlying neural correlates for impaired inhibitory control are posited to be frontostriatal circuits which include the dorsolateral prefrontal cortex, dorsal striatum, and thalamus with modulatory input from the cerebellum.

B2. Emotional Processing and Impulsivity: An Alternative Model of ADHD

Central to this research proposal is the hypothesis that in addition to abnormalities within FS circuits, abnormalities within FL circuits also play a significant role in symptom formation for some children with ADHD. This hypothesis is based on an emerging body of research from a broad range of experimental approaches. To begin, children with ADHD are known to display frequent, poorly regulated outbursts of emotion and, indeed, the DSM-IV includes affective symptoms as an associated feature of the disorder, and earlier versions of the DSM included them as part of the diagnostic criteria. Likewise, epidemiological studies...
conclude that children with ADHD have elevated rates of mood disorders, substance use disorders, and antisocial behaviors\textsuperscript{26-28}. Whereas deficits in inhibitory control and associated FS circuits may underlie these comorbid mood and behavioral symptoms for some children with ADHD\textsuperscript{16}, for others these behaviors are likely related to deficits in the functioning of affective circuits\textsuperscript{7, 20}. For example, altered emotional processing in children with ADHD is evidenced in distorted appraisals of affective stimuli\textsuperscript{29, 30}, poor emotional regulation\textsuperscript{31-33}, atypical conditional learning\textsuperscript{34}, and aberrant approach and withdrawal behaviors\textsuperscript{11, 35}.

Our investigation of emotional processing in children with ADHD focuses on the two affective dimensions specified by the Circumplex Model of Affect – valence and arousal\textsuperscript{36}. By valence, we mean the positive or negative felt quality that is inherent to all emotional experiences\textsuperscript{37, 38}. By arousal, we mean the preparedness of an organism for action\textsuperscript{39}. Levels of arousal can range from coma or sleep on one extreme, to intense excitement or panic on the other\textsuperscript{36}. These two affective dimensions form a circular array (i.e., a circumplex) of emotional labels representing a pleasure-displeasure, or approach-withdrawal, continuum along the valence dimension and an arousal level along the other. Every affective experience is then the linear combination of these two underlying dimensions, valence and arousal\textsuperscript{36}, that two corresponding and underlying neurophysiological systems subserv\textsuperscript{4, 40}. The physical sensations that these two systems produce are interpreted, and emotional labels are assigned, based on a cognitive appraisal of the context and stimuli that may have incited them\textsuperscript{40}.

In the current proposal, we will measure brain activity associated with self-rated emotional experiences that are generated in response to the viewing of emotion-denoting words during the performance of the Affective Circumplex Task. Participants will rate their own emotional experiences along the valence and arousal dimensions and correlations between fMRI signal and these affective ratings will be obtained. We hypothesize that children with ADHD compared with healthy controls will demonstrate neural activity that is a) progressively more exaggerated for progressively more positively or negatively valenced emotional states, and also b) progressively more exaggerated for progressively more arousing states. In other words, for ADHD youth the neurophysiological systems that underlie valence and arousal sensations predispose these children to highly (positively or negatively) valenced and highly arousing emotions. Highly charged emotions are exceedingly common in ADHD youths\textsuperscript{16}. Indeed, the primary concern that often leads parents to bring children with ADHD to treatment is struggles with rage and frustration - negatively valenced, highly arousing emotions - and these types of emotional reactions often cause children with ADHD significant impairments in social functioning\textsuperscript{41, 42}. At the same time, ADHD youth are often described as “spirited”\textsuperscript{43} with an abundance of enthusiasm and energy, which are positively valenced and arousing emotions\textsuperscript{4, 36}. (ADHD children often complain that treatment with psychostimulants diminishes these positive sensations.) Self-reports and observational studies of emotional states in children with ADHD compared with healthy peers concur with this, as the ADHD children demonstrate more frequent displays of highly arousing emotions\textsuperscript{34}, more sensation-seeking behaviors\textsuperscript{35}, and greater self-reported reactivity to positive stimuli\textsuperscript{35, 45}. Conversely, low arousal, relatively neutral valence states (such as calmness) are less common in ADHD youth\textsuperscript{16, 46} and we suspect that is because of their high valence, high arousal emotional reactivity. In this emotion-driven model of ADHD, the highly charged affective responses of ADHD youth draw attentional resources away from the mundane to the exciting. Therefore, children with this affective style can exhibit impulsive behaviors and symptoms similar to those displayed by children with impaired inhibitory control; however, the neural substrates for their symptoms are posited to be related, at least in part, to altered activity in valence and arousal circuits, rather than solely to disturbances in inhibitory/FS circuits.

Figure 2 is presented to help clarify our hypothesized results. In the arousal dimension, we postulate a linear relationship between arousal ratings and fMRI signal, such that increasing arousal will accompany increasing fMRI signal. The slope of the line indexing this association will be steeper in children with ADHD as compared with healthy control children indicating greater increases in fMRI signal per unit arousal in the ADHD as compared with control population (see Figure 2A). Similarly, in the valence dimension, we postulate a linear relationship between valence ratings and fMRI signal; however, we will assess the correlations of fMRI signal with the extremes of emotional valence, as indexed by the absolute value of the valence ratings. This analysis is undertaken in light of numerous findings from animal studies of emotional processing in which subcortical brain regions contained distinct but intermingled populations of neurons, one determining positive valence and another determining negative\textsuperscript{47}. These findings suggest that, for a given brain region, fMRI signal may increase with progressive increases in either positive or negative valence\textsuperscript{46}. This generates a V shaped relationship...
between valence and fMRI signal with increases in fMRI signal accompanying increases in either positive or negative valence. We hypothesize that this V shaped relationship between valence and fMRI signal will be sharper in children with ADHD as compared with health control children indicating a greater increase in fMRI signal per unit valence in the ADHD as compared with control population (see Figure 2B).

**Figure 2A**

![Graphical representation of our hypothesized results. 2A.](image)

**Figure 2B**

![Graphical representation of our hypothesized results. 2B.](image)

During the Affective Circumplex Task, participants rate along the valence and arousal dimensions their own emotional responses to emotion-denoting words. This approach raises important questions:

1) Why use words as the emotional stimuli?

Words were selected as the affective stimuli because the emotional response to a word is typically congruent with the emotion associated with the word. By using words and instructing participants to reflect upon the emotion they associate with the word, we are assigning participants with the task of rating their own emotional experience. Conversely, facial expressions and other affective stimuli are more apt than emotion-denoting words to generate feelings in the viewer that are incongruent with the emotion depicted in the stimulus. For example, a facial expression depicting anger might induce feelings of fear in the viewer. This can potentially confound the imaging results as it may be unclear what emotion the participant is rating (i.e. his own or what he perceives in the facial expression that he is presented with). Moreover, if there is incongruity between the emotion that is presented in the stimulus and the emotion that the viewer feels, this creates an additional task burden; the participant must attend to two different emotions, and rate only one. The incongruity between self and stimulus requires inhibitory control for the participant to rate correctly his own emotional experience and not the emotion portrayed in the stimulus. A central aim of this study is to dissociate inhibitory control from emotional reactivity, and thus we have selected our emotion task such that it requires as little inhibitory control as possible.
2) Why not investigate reward processing instead of emotional reactivity?

Several studies investigating reward-based decisions suggest that children with ADHD have atypical reward gradients such that the subjective value of future rewards decreases over time more steeply in children with ADHD as compared with their peers\(^4^9\). Investigators have thus suggested that children with ADHD have a stronger aversion to delayed gratification than their peers and that this aversion is independent of poor inhibitory control, even though it produces similar impulsive behaviors\(^5^0\). Such studies implicate affective circuits in the neurobiological underpinning of ADHD, but more specific neural correlates are unknown. Some investigators, for example, point to an increased sensitivity to rewards in ADHD children\(^5^1\), whereas others describe a relative indifference to rewards\(^5^2\). In a recent fMRI study, adolescents with ADHD were found to have a neural hypo-responsiveness to anticipated reward and the authors suggest this may underlie the participants' behavioral hyper-responsiveness to the same stimuli\(^1^2\). Reward circuits alone are unlikely to fully explain the atypical behavioral reward gradients evidenced in ADHD youth\(^5^3\). Indeed, the presence of delay aversion suggests not only an atypical sensitivity to reward, but also a heightened aversion to waiting. Unlike reward processing tasks, the Affective Circumplex Task investigates emotional experiences ranging from negative to positive valence (i.e. both reward and aversion) and enables examining valence as one continuum (displeasure to pleasure) or also as two distinct components (separate neural correlates of positive and negative valence). In sum, the behavioral observation that ADHD youth have atypical responses to rewards is inherently confounded by impulsivity, altered reward sensitivity, and delay aversion. FMRI tasks investigating reward processing cannot readily disentangle one effect from another.
D. RESEARCH PLAN

D1. To meet all of the study’s aims and adequately test the hypotheses, I plan to obtain fMRI scans and behavioral measures on 60 children in total - 30 with ADHD and 30 healthy controls. The fMRI scans will be acquired during the performance of the Simon Task and Affective Circumplex Task. The behavioral measures will include diagnostic and demographic assessment measures as well as a neuropsychological battery. During years 1 through 4 of the project, the behavioral and neuroimaging data will be collected and the imaging data will be processed as it is acquired to ensure the quality and stability of imaging data. During years 4 and 5, statistical analyses will be conducted on both the imaging and behavioral data. Additionally, during years 4 and 5, I will focus on interpreting the results and preparing manuscripts for publication of the study’s findings. Lastly, data gathered from this study will guide the design and implementation of a larger, prospective study for a R01 application that I will submit during Year 5 of the award period. The focus of the follow-up study will be guided by the findings from the current proposal; however, if the hypotheses for the current study are upheld, then I will propose a longitudinal study to investigate the developmental trajectory of the functioning of FS and FL circuits in ADHD youth. The aim of this study will be to determine whether functional abnormalities in these circuits inform the development and clinical course of ADHD.

D2. Developmental Considerations with Regard to the Age of the Sampled Population

Characterizing neural abnormalities early in the course of psychiatric disorders is vital in differentiating what may be underlying neural causes of the disorder from the brain’s adaption to living with the disorder61. This is all the more true of childhood onset disorders because of the remarkable plasticity of the developing brain65-67. With some notable exceptions68, functional neuroimaging studies of ADHD have focused largely on adolescence69, 70 and adulthood71, 72, whereas ADHD is a developmental disorder emerging most commonly during the early school age years16. By studying ADHD youths at ages 8-12, we have selected an age group that is most likely to be just coming to clinical attention for ADHD, is under-represented in the extant neuroimaging literature, and is an age group that can be recruited prior to being treated with any psychotropic medications. Additionally, by investigating neural abnormalities that present early in the course of the disorder, we may be able to uncover susceptibility factors that predict subsequent disease course. Verifying this would require longitudinal follow-up to the current study and developing the expertise to conduct such a study is part of this award’s training plan (see Training Goal 4).

D3. Sample The sample size will include 60 children with (N=30) and without (N=30) a diagnosis of ADHD-Combined Type (age range 8 to 12 years).

Inclusion criteria for the subjects with ADHD will include DSM-IV criteria for ADHD - Combined type (ADHD-C). Two child psychiatrists will review the diagnostic and neuropsychological assessments for each subject independently. Their concordance will be evaluated throughout the award period to insure strong inter-rater agreement (i.e. kappa>0.80). Where the two diagnosticians disagree the case will be discussed and if consensus cannot be achieved without difficulty (e.g., one of the diagnosticians misread a report), the case will be excluded.

Exclusion criteria for control subjects will include any active DSM-IV Axis I psychiatric disorders or any history of ADHD, oppositional defiance disorder (ODD), or conduct disorder (CD).

Exclusion criteria for ADHD subjects will be similar, with the exception of ADHD-C, ODD and CD. ODD and CD are highly co-morbid with ADHD16 and therefore will not serve as rule outs but will be assessed and covaried for in our analyses. ADHD subjects will be excluded if they have ADHD subtypes other than Combined Type or if they have had prior treatment with a psychostimulant medication8.

8 Recruiting children with ADHD who have no prior exposure to psychostimulants may present a challenge. However, given that the study mentors have extensive experience with recruitment of ADHD patients and that the clinics at Columbia University have a high patient volume (over 2000 new patients per year), we do not anticipate this being a significant hurdle. Should this prove to be more difficult than anticipated, ADHD participants on psychostimulants could
Additional exclusion criteria for both groups will include: (1) age < 8 or > 12; (2) neurological illness or significant head trauma (loss of consciousness > 2 minutes); (3) serious medical problems; (4) pregnancy or planned pregnancy during the study period; (5) currently taking medications that have CNS effects (e.g. antidepressants, neuroleptics, seizure medications, drugs that affect blood pressure or heart rate, alpha-agonists, adrenergic blockers, lithium, sedating antihistamines, and some medications for treatment of asthma). (6) IQ < 80; (7) reading level below 2nd grade and (8) irremovable metal on the body such as braces.

D4. Recruitment Youth will be recruited through a combination of the following means: (a) public advertisements; (b) clinic outreach through the Columbia University pediatric and psychiatric clinics (in total averaging over 2000 new patients per year); and (c) direct mailings to and phone contact with participants in studies on youth with ADHD currently being conducted by Drs. Bradley Peterson and Laurence Greenhill. Additionally, the P.I. (Dr. Jonathan Posner) will work 4 hours per week in the ADHD clinic at the Columbia University Children’s Hospital of New York (see training goal 2, Career Development/Training Activities) and will work with staff at the clinic to recruit potential participants. Dr. Greenhill has worked on NIMH multi-site clinical trials of treatments for children with ADHD, including the Multimodal Treatment Study of ADHD (MTA Study), and the Preschool ADHD Treatment Study (PATS). For these studies, the Columbia University site met within 24 months its recruitment goals of 96 school age children with moderate to severe ADHD, Combined Type. We therefore do not anticipate difficulty in achieving the recruitment goal of 30 medication-naive youths with ADHD over 5 years for the proposed study.

Healthy control youth will be recruited from community-based telemarketing lists of households characterized by zip code, age, gender, ethnicity, and income level (Donnelley Marketing, ph: 1-800-846-7338). Introductory letters will be sent to households within same zip code as the ADHD participants to recruit a control sample with a demographic profile that matches the clinical sample. These mailings will be followed up by phone calls that describe the study and address questions in detail. Using these same recruitment methods in the past, approximately 10% of eligible control families contacted have ultimately participated in studies conducted in Dr. Peterson’s laboratory.

D5. Screening During a preliminary phone screening, potential subjects will be informed that the study will include a MRI scan and will be asked if they have any metal on or in their bodies that would preclude them from participating. Eligible participants will then be scheduled for a 2-hour semi-structured diagnostic and neuropsychological assessment. If subjects continue to meet inclusionary criteria after the diagnostic/neuropsychological assessment, they will be scheduled for a 1-hour MRI scan.

The diagnostic and neuropsychological assessment will be performed by a trained research assistant (RA, hired for this grant). A developmental neuropsychologist working in Dr. Peterson’s lab will assist in training and supervising the RA on all diagnostic and neuropsychological measures. As the P.I. (Dr. Jonathan Posner) becomes proficient with the diagnostic measures (see training goal 2, Career Development/Training Activities), he will supervise the RA on these assessments. All assessments will take place in neuropsychological testing suites at the New York State Psychiatric Institute.

Diagnostic Assessment: The following battery of structured and semi-structured interviews will be used to establish the diagnosis of ADHD-C and assess for comorbid conditions. With the exception of the teachers’ assessments (number 3 below), all measures will be obtained during the diagnostic and neuropsychological assessment session.

1. General Measure: Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) Present and Lifetime Version is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria. We will include the newly added K-SADS module to evaluate for Autism spectrum disorders.

be included and MRI scanning would be done after a sufficient medication wash-out period (i.e. 4-5 half lives). This would be noted and covaried for in subsequent analyses.
2. **ADHD Rating Scales:** Parents will complete the *Conners’ Parent Rating Scales 3rd Ed.: Long Version*\(^7\) (a 110 item questionnaire with 10 subscales assessing primary ADHD symptoms and common co-morbidities), the *DuPaul-Barkley ADHD Rating Scale: Home Version*\(^7\) (a 14-item parent questionnaire modeled after DSM-IV criteria for ADHD), and the *Child Behavior Checklist*\(^6\) (a 113 item questionnaire assessing behavioral problems using a 3-point scale for each item.)

3. **Teachers** will be asked to complete the *Conners’ Teacher Rating Scales 3rd Ed.:Long Version*\(^7\) and the *DuPaul-Barkley ADHD Rating Scale: School Version*\(^7\). (These measures will be mailed to potential participants’ teachers following the initial telephone screening. The diagnostic & neuropsychological assessment session will not be scheduled until these completed measures have been obtained. Prior experience from the study mentors suggest that obtaining these measures will not be overly burdensome.)

4. **Comorbid Mood Symptoms** Current levels of depression will be assessed using the *Children’s Depression Inventory*\(^77\) (a 27-item, self-report instrument for measuring the severity of depression). Anxiety will be assessed using the *Revised Children’s Manifest Anxiety Scale*\(^76\) (a 37-item anxiety scale divided into three anxiety subscales and one lie subscale). Manic symptoms will be assessed using the *Young Mania Rating Scale*\(^79\) (an 11-item questionnaire for measuring the severity of manic symptoms in pediatric populations ages 5 through 17). The *Children’s Yale-Brown Obsessive Compulsive Symptom Scale* (CY-BOCS)\(^80\) assesses for symptoms of pediatric obsessive-compulsive disorder (OCD) and will be used to evaluate for the presence of these comorbid symptoms in the youths participating in this study.

5. **Substance Abuse:** Youths will be given the Brief Lifetime version of the *Customary Drinking and Drug use Record*\(^81\) to assess lifetime alcohol, marijuana, nicotine, and other drug use.

**Neuropsychological and Clinical Assessments** The following measures will be collected either before or after, but always on the same day as, the MRI scan. The measures will be used to assess general cognitive functioning, as well as inhibitory control processes and emotional reactivity. This will permit hypothesis testing for Aim 3 - To examine associations of activity in FS and FL circuits with measures of cognitive and emotional functioning and symptom severity in children with ADHD.

1. **Intellectual functioning** will be assessed prior to the MRI scanning using the two-subtest form of the *Wechsler Abbreviated Scale of Intelligence (WASI)*\(^82\) to provide a quick screening estimate of participants’ intellectual functioning. This short form includes one verbal test (Vocabulary) and one nonverbal test (Matrix Reasoning). Reading level will be determined using the *Woodcock Reading Mastery Tests-Revised*\(^83\). A reading level of 2nd grade or above is necessary for participants during the Affective Circumplex Task.

2. **Handedness** *Edinburgh Handedness Inventory*\(^84\) is a standard self assessment of dominance for hands, feet, and eyes.

3. **Socioeconomic status** of each participant’s family will be assessed with the *Hollingshead Index of Social Status*\(^85\).

4. **Pubertal Assessment** Pubertal stage may impact neural function particularly in the prefrontal cortex\(^86\). In order to provide an estimate of pubertal development, the *Pubertal Development Scale* (PDS)\(^87\) will be administered to each participant. The PDS is a 5-item self-report measure of pubertal status with demonstrated reliability and validity. The PDS correlates significantly \(r = 0.61 – 0.67\) with both physician ratings and Sexual Maturation Scale (Tanner) self-ratings of pubertal maturation\(^88,89\).

5. **Inhibitory Control** – During scanning sessions, ADHD subjects and healthy children will perform the *Simon Task* (see Imaging Procedures Section) that will provide behavioral measures of inhibitory control. Additionally, performance measures of inhibitory control will be obtained outside of the MRI scanner using the *Conner’s Continuous Performance Task (C-CPT)*\(^90\). This task requires participants to provide a rapid, simple response when certain stimuli appear while forgoing any response when other stimuli are presented. Commission errors (i.e. responding to non-target stimuli) index inhibitory control. A recent meta-analysis of 40 studies demonstrate an average effect size of \(d=0.55\), comparing commission errors in ADHD subjects with controls\(^91\). Participants will perform the C-CPT during the neuropsychological assessment.

6. **Emotional Reactivity** – We will use the following parent and teacher report assessment tools of emotional reactivity.
A. **Strengths and Difficulties Questionnaire** (SDQ)\(^{92}\) is a 25 item parent report measure developed to assess emotional and behavioral problems with strong psychometric properties ranging in children from ages 4 to 17 years. We will use the emotional problems subscore as an assessment of clinical relevant emotional reactivity.

B. **Conners’ Parent and Teacher Rating Scales** We will use the emotional lability subscales as an assessment of emotional reactivity.

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**D6. Imaging Procedures**

**Subject Preparation** Scan sessions will occur on the same day as neuropsychological testing. Frequent praise, reminders to remain still, and relaxation training, along with an inflation pillow and taping of the subject’s forehead, will help to acquire motion-free images. In the past 15 years, the Pediatric Brain Imaging Laboratory has acquired superb, motion-free scans in over 1200 young children and adolescents and over 800 adults affected by a variety of neuropsychiatric illnesses (including ADHD and Tourette syndrome).

**Whole Body 3T MRI Scanner** Images will be acquired at the New York State Psychiatric Institute on a GE Signa 3T whole body scanner. The Signa 3.0 Tesla magnet, with a 55cm diameter patient bore, is a high homogeneity, actively shielded, wide-bore superconducting system, utilizing single cryogen unit technology. The magnet delivers high, uniform homogeneity (<0.05ppm on water spectral FWHM for 20cm DSV), which is essential for superior data quality in demanding imaging techniques. The scanner is equipped with the highest performance (CRM) Shielded Gradient Coil enabling techniques such as ultra-fast echo-planar imaging. The gradients have maximum amplitude of 40mT/m with a Slew Rate as high as 150 mT/m/s. The scanner hardware and software have been upgraded to a GE 32-channel receiver hardware platform, 15M4 software platform, and ASSET (Array Spatial Sensitivity Encoding Technique) software. The 32 high bandwidth receivers, along with ASSET, deliver cutting-edge parallel imaging by making possible dramatically shortened TRs, TEs, and ESPs. Signal-to-noise is enhanced by up to 5 times over the prior LX platform, susceptibility artifacts are further suppressed, and resolution has been enhanced by the same proportion as a result of the multichannel receiver capability.

**MRI Pulse Sequences** T1-weighted sagittal localizing images will be acquired followed by a 3D spoiled gradient recall (SPGR) image for coregistration with axial echoplanar images. Axial echoplanar images (TR = 2200 msec, TE = 25 msec, 90° flip angle, single excitation per image, slice thickness 3 mm, 24 x 24 cm field of view, 64 x 64 matrix, no skip) will be obtained to provide an effective resolution of 3.75 x 3.75 x 3.5 mm and whole brain coverage. All image acquisition will be reviewed by a neuroradiologist for any suspected anatomical abnormalities. **Total scan time** per session will be approximately 60 minutes.

**Simon Task** A series of white arrows pointing either left or right is displayed against a black background either to the left or right of a white gaze fixation cross-hair positioned at midline. Stimuli will be ‘congruent’ (arrows pointing in the same direction as their position on the screen) or ‘incongruent’ (pointing in a direction opposite their position on the screen). Subjects will be instructed to respond as quickly as possible to the direction of the arrow by pressing a button on a response box. The button press will record subject responses and reaction times for each trial. Stimulus duration will be 1300ms, with jittered inter-stimulus intervals ranging from 4 to 7 seconds. Each run will contain 55 stimuli with equal numbers of congruent (22) and incongruent (22) stimuli, in addition to 11 fixation stimuli. In each run, 11 arrows will be left-pointing and 11 will be right-pointing; 11 will appear to the left of midline and 11 to the right. Half the incongruent stimuli will require the same response as the preceding congruent stimulus. Each experiment will contain 3 runs (5 min, 21 sec per run), totaling 66 incongruent and 66 congruent stimuli.

**Affective Circumplex Task** Each trial is 38 seconds in duration and consists of three distinct temporal components: (1) participants are shown a single emotion-denoting word for 18 s, having been instructed before the experiment to reflect upon the emotion that the word described; (2) they are then shown a 9 x 9 grid displaying the dimensions of valence and arousal as visual analog scales on the x- and y-axes, respectively, ranging in values from -4 to +4; (3) they will then gaze at a cross-hair at the center of an otherwise blank screen for variable durations, such that the time from offset of the prior word to presentation of the next word (i.e., the total time for rating of valence and arousal, followed by gaze fixation) equals 20 s. The 9 x 9 grid used to collect affective ratings allow participants to rate simultaneously both valence and arousal with a single click
of the mouse. Before the scanning session, each participant will practice a shortened version of the task using a different set of stimuli outside of the scanning environment. Participants will be instructed to try to generate the feelings described by the emotion-denoting words and to rate the feelings using the 9 x 9 grid. Participants will be given the following written instructions: “You will be shown words that describe certain emotions. Try to think about what the emotion feels like. Some people think about situations that have made them feel the emotion in the past.” Prior behavioral studies have shown that the 9 x 9 affective grid provides ratings of valence and arousal similar to those obtained when these two affective dimensions are rated separately. Each experiment will contain 3 runs (10 min, 28 sec per run) with a total of 48 stimuli and associated ratings per subject.

**Image processing** Image processing and statistical analyses will employ SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Slice-timing correction will be applied and images will be motion-corrected for three translational directions and rotations. Motion parameters will be entered as covariates into each subject’s design matrix to control for motion-correlated signal changes. Corrected images will be spatially normalized to the standard MNI template using a hybrid algorithm of affine transform and nonlinear warping. Normalized images will then be spatially filtered with a Gaussian filter having a full-width, half maximum of 6 mm. A discrete cosine transform-based high-pass filter with a basis function length of 128 seconds will be used to remove drift from the baseline image intensity. As specified below, contrast images for each subject will be generated and entered into group level analyses (see below under Biostatistics and Hypothesis Testing for a more detailed description).

**Regions of Interest** For FS circuits, the regions of interest (ROIs) will include the dorsolateral prefrontal cortex, dorsal ACC, dorsal striatum (caudate and putamen), and thalamus. For FL circuits, the ROIs will include the medial prefrontal cortex, rostral ACC, ventral striatum (including the nucleus accumbens), amygdala, and hippocampus. The ROI masks will be selected from the Wake Forest University ROI library, WFU_PickAtlas (http://fmri.wfubmc.edu). Given our *a priori* hypotheses regarding FS and FL circuits, group level analyses will be limited to pre-specified ROIs and small volume corrections will be applied.

**D7. Data Management**

**Clinical and Neuropsychological Data:** The PI (Dr. Jonathan Posner) will design a password protected database in Microsoft Access that will be stored on a server securely located behind the NYSPI/CU network firewall. Data will be entered twice and checked for consistency. Participants will be identified by numeric codes consistent with HIPAA guidelines; hard copies of data that could identify subjects will be stored in locked locations with restricted access. Server backups containing study databases will be performed nightly; database copies on CD-ROM archive disks will be stored separately for safety.

**Imaging Data Management:** Imaging data will be controlled for quality at the scanning console under the supervision of Alayar Kangarloo, Ph.D. (Physicist, Columbia University MRI Unit), then transferred to Dr. Jonathan Posner’s computer over a dedicated fiberoptic network (data transfer rate of 1 GBits/second) through a Storage Area Network (SAN). This high speed, password protected system supports disk mirroring, backup and restore, archiving, retrieval of archived data, data migration from one storage device to another, and data sharing among different servers.

**D8. Biostatistics and Hypothesis Testing**

**Aims 1 and 2:** To measure and compare brain activity in children with ADHD with that of age-matched control participants during the performance of the Simon and Affective Circumplex Tasks.

**Hypotheses 1** maintains that during the performance of the Simon Task, children with ADHD, as compared with healthy children, will have reduced task related activations in the frontostratial circuits that subserve inhibitory control. Time series data for each subject will be entered into individual subject-level analyses using the general linear model. Contrast images for each subject will be generated, indexing voxel wise signal differences across congruent and incongruent trials. Hypotheses 1 can be then tested by entering the contrast images for each subject into a group-level analysis using the following regression model: \( Y_j = \beta_{0j} + \beta_{1j} Gp_j + \epsilon_j \). In this model, \( Y_j \) denotes the dependent variable: the average task-related signal change in each voxel within
the predefined frontostriatal ROIs for the \( j \)-th subject, where \( j = 1, \ldots, 60 \). The frontostriatal ROIs will index signal differences across congruent and incongruent trials from the Simon Task. \( \beta_0 \) is the random intercept for subject \( j \); \( \beta_1 \) is the regression coefficient for the term representing the effect of diagnosis on subject \( j \); \( G_p \) is a dummy variable representing diagnostic group membership (i.e. children with or without ADHD); and \( \varepsilon_i \) is the error term. (Other subject characteristics such as gender and age will be included in the model, but are disregarded for this power analysis.) The null hypothesis, \( H_0: \beta_1 = 0 \), holds that the diagnostic group does not influence the dependent variable and following a significant omnibus F test, a t-test can be applied.

Hypothesis 2 maintains that during the Affective Circumplex Task, children with ADHD, as compared with their healthy peers, will have neural activity in the frontolimbic circuits that is a) progressively more exaggerated in association with progressive increases in self-reported positive or negative valence, and also b) progressively more exaggerated in association with progressive increases in self-reported arousal. To test this hypothesis, for each subject we will model the time series data with six predictor variables and a constant. The predictor variables will include: (1) the canonical hemodynamic response function (cHRF) convolved with a box car function (BCF) of 18 s duration indexing the presentation of the affective stimulus (we will term this function A); (2) Function A weighted by the arousal rating for each stimulus; (3) Function A weighted by the valence rating for each stimulus; (4) Function A weighted by the absolute value of valence rating for each stimulus; (5) the cHRF convolved with a BCF indexing the presentation of the 9 × 9 response grid, and (6) the cHRF convolved with a BCF indexing gaze fixation. Voxel-based correlation estimates for each subject will be entered into group-level analyses to compared signal change between ADHD children and healthy controls. Group comparisons will be made by conducting three independent sample T tests using the regression coefficients derived from predictor variables 2 (arousal ratings), 3 (valence ratings), and 4 (absolute value valence ratings) derived from children with and without ADHD.

**Power analysis for Aims 1 & 2** For Aims 1 and 2, with 60 subjects and \( \alpha = 0.05 \), there is sufficient power (80%) to detect a medium effect (\( f^2 = 0.14 \)).\(^c\)

**Aim 3** To examine associations of activity in FS and FL circuits with measures of cognitive and emotional functioning and symptom severity in children with ADHD.

Hypothesis 3A maintains that a double dissociation will be found in the behavioral correlates of FS and FL circuits during the performance of the Simon and Affective Circumplex fMRI Tasks. Hypothesis 3A will be tested in 2 steps:

1. We will determine whether abnormal frontostriatal activity during the Simon Task accompanies poorer performance on behavioral measures of inhibitory control but not emotional reactivity. To test this hypothesis, we will calculate Pearson’s correlation coefficients for the association of: A) behavioral measures of inhibitory control with signal changes in predefined frontostriatal ROIs; and B) behavioral measures of emotional reactivity with signal changes in predefined frontostriatal ROIs. **Hypothesis 3A** maintains that a significant correlation will be found for A, but not B.

2. We will determine whether abnormal frontolimbic activity during the Affective Circumplex Task accompanies abnormal measures of emotional reactivity but not poorer performance on measures of inhibitory control. Similar to the statistical method used in Step 1, we will calculate Pearson’s correlation coefficients for the association of: A) behavioral measures of inhibitory control with signal change in predefined frontolimbic ROIs; and B) behavioral measures of emotional reactivity with signal changes in predefined frontolimbic ROIs. **Hypothesis 3A** maintains that a significant correlation will be found for B, but not A.

Hypothesis 3B maintains that activity in FS circuits will mediate the relationship of an ADHD diagnosis with behavioral measures of inhibitory control and that activity in FL circuits mediates the relationship between the

\(^c\) Because the proposed project is a pilot study, it is powered to detect only ‘medium’ effect sizes between children with and without ADHD. The analyses from this project will inform later work, which will be powered to detect small effect sizes.
diagnosis of ADHD and behavioral measures of emotional reactivity. Hypothesis 3B will be tested using mediator analyses combining neuropsychological profiles and imaging data. Mediator analyses try to identify the mechanisms that bring about a relationship between the dependent and independent variables by including a third explanatory variable, known as a mediator variable. These analyses permit stronger causal inferences than do simple bivariate correlations. Mediator analyses provide a powerful tool to study brain-behavior correlations. In the Peterson brain imaging laboratory, we have recently used mediator analyses beneficially, for example, to study brain-behavior correlations in persons at differing levels of familial risk for developing major depression.

Mediator analyses will permit us to test whether fMRI signal (the mediator variable, M) mediates the relationship between the diagnosis of ADHD (the dependent variable, Y) and abnormal behavioral measures of inhibitory control and emotional reactivity (the independent variables, X). We will test our mediator hypotheses using a series of standard regression analyses applied to the pre-defined ROIs. We will test the statistical significance that variable M mediates the association between an independent variable, X, and the dependent variable, Y, using three regression equations: (1) \( Y = i_1 + cX + e_1 \); (2) \( Y = i_2 + cX + bM + e_2 \); and (3) \( M = i_3 + aX + e_3 \) where \( i_1, i_2, \) and \( i_3 \) are intercepts, \( a, b, \) and \( c \) are regression coefficients, and \( e_1, e_2, \) and \( e_3 \) are error terms for the regressions. Testing the statistical significance of the hypothesized mediation requires demonstrating the significance of both the coefficient \( c \) (using a t-test in the linear regression setting) and the product \( ab \) (also using a t-test, which we approximate as \( \frac{ab}{\sqrt{b^2 \sigma_a^2 + a^2 \sigma_b^2}} \), where \( \sigma_a^2 \) and \( \sigma_b^2 \) are the standard deviations of \( a \) and \( b \) estimated from the corresponding linear models). The statistical significant of these mediation effects are assessed by plotting the p-value for \( ab \) within each pre-defined ROI.

Hypothesis 3C maintains that fMRI measures of abnormal functioning of FS and FL circuits will have a cumulative influence on ADHD symptom severity. Hypothesis 3C will be tested using stepwise regression analysis to demonstrate that ADHD symptom severity (as measured by the Conner’s ADHD subscale of total ADHD symptom severity) is better accounted for when the influence of abnormal functioning within both FS and FL circuits is considered, rather than considering the influence of FS or FL circuits alone. The following regression equation will be used: \( Y_j = \beta_{0j} + \beta_{1j} FS_j + \beta_{2j} FL_j + \epsilon_j \). In this model, \( Y_j \) denotes the dependent variable; ADHD symptom severity for each participant, where \( j = 1, ..., 60 \). \( \beta_{0j} \) is the random intercept for subject \( j \); \( \beta_{1j} \) and \( \beta_{2j} \) are the regression coefficients for the term representing signal changes within the predefined frontostriatal and frontolimbic ROIs, respectively, and \( \epsilon_j \) is the error term. Hypothesis 3C maintains that \( \beta_{1j} \) and \( \beta_{2j} \) represent statistically significant regression coefficients and that the regression equation that includes both independent variables (i.e. frontostriatal and frontolimbic ROIs) accounts for more variance (i.e. greater \( R^2 \)) than comparable equations that include only one, or the other, of the two independent variables.

Power analysis for Aim 3 For Aim 3, with 60 subjects and \( \alpha = 0.05 \), there is sufficient power (80%) to detect a medium to large effects (\( \hat{f}^2 = 0.19 \)).

Assessment of potential confounds For each of the regression models, potential confounds such as handedness, IQ, socioeconomic status, and minority status will be entered as covariates. If no significant main effects or interactions are detected and if the measures have negligible effects on the other parameter estimates, they will not be included in the final regression models.