Brain Indices of Stimulant Treatment in Drug-Naive Youth at Risk for Substance Use Disorder

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INTRODUCTION TO REVISED APPLICATION

We thank the reviewers for their thoughtful feedback and positive comments about the significance of the project, the team's qualifications and our research environment. They also had some concerns, which we have addressed in the revised proposal and below.

Significance:

Rev. 3 (R3): "premise for the … between-group difference in reward-induced activation of insular and ventral striatum is not sufficiently elaborated." Refs 16 & 17 do not support hypothesis of changes in ventral striatum.

Response: We have revised hypotheses regarding the insula but not the ventral striatum based on new preliminary data showing between-group activation differences in insula, putamen and ACC (not ventral striatum) in high-risk (HR) vs. low-risk (LR) and control groups (see section C.3.3. Preliminary Studies).

R3: "The need for the formulation of two mutually exclusive hypotheses (HR>LR and LR>HR) is not clear."

Response: We have clarified our aims and hypotheses to focus on single hypotheses: 1) group differences in baseline activation (We hypothesize HR>LR based on new preliminary data), and 2) group differences in effect of MAS-XR (We hypothesize greater reduction in activation for the HR vs. LR groups).

Investigator(s):

R2: Since Dr. Fan is not listed under key personal, "concern that expertise with ACR is lacking." "Is there a member of the team qualified to administer the ACR task?"

Response: Dr Fan is added as key personnel. Dr Ivanov also has extensive experience administering ACR in children and will train a research associate to run ACR training of study participants.

Approach:

R1, R3: concern regarding whether 3 week post-treatment is sufficient to show changes in reward response. Rationale for 3 week period is based on pre-clinical study."

Response: There are no published data regarding treatment effects on activation of the brain reward system. We will test for changes following 3 weeks of stimulant treatment, which has produced changes in activation in adults with ADHD (Yang et al., 2016, ref 66 in the proposal).

R1: concern re: possible confounding effects of family history of SUD (allowed in the high risk but not low risk group.

Response: Ideally we might add a positive family history-only group, but this would exceed the scope of a pilot/feasibility study. We will therefore exclude SUD family history for the LR and HR groups.

R1: Much of the inclusion and exclusion criteria and recruitment/retention strategies were in Human Subjects.

Response: This is now included in the main document.

R1: Unequal number of males and females will be recruited, no analysis of sex effects.

Response: Sex will be included as a covariate.

R1: Practice effects are not discussed.

Response: Prelim. data (4 subjects scanned 2X with no intervening intervention) show no practice effects.

R2: Preferable to pre-specify the washout period for all subjects on non-stimulant treatments.

Response: A 2-week washout period is now specified.

R2: Inconsistency regarding family history of SUD in 1st degree relatives (pg 53 vs. C.2.2).

Response: We clarified that FH is excluded in both the HR and LR groups.

R2: Reference is made to pilot data, but a small section on Preliminary Studies is included with no data.

Response: We now include a graph summarizing our preliminary data.

R3: The power analysis is not sufficiently elaborated.

Response: We revised the power analyses section.

R3: The section "Dose titration" indicates that some patients may receive different doses of MAS-XR. No statistical control for dose variation is proposed.

Response: A variable for dose is now added into the analyses.

R3: outcome changes might be a result of the acute and/or extended effects of treatment. Time from the last medication dose and the scan is not provided.

Response: There will be a ≥6-8h interval between drug administration and scanning (now specified). Thus, ation changes detected on 2nd scan will reflect changes during treatment rather than acute drug effects.

inor: a number of mistakes/typos.

Response: They have been corrected.

Among youth with vulnerability for the development of substance use disorders (SUD), those with attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) or severe oppositional defiant disorder (ODD) are considered to be at highest risk[1]. Stimulants such as methylphenidate (MPH) and mixed amphetamine salts (MAS), and a variety of non-stimulants, have established efficacy for ADHD - but response is greater for stimulants than non-stimulants[2]. Basic science studies have shown sensitizing effects of MPH on the brain reward system[3] in animal models of SUD risk[4,5], with MPH-exposed animals having greater self-administration of cocaine[6] – which is a cause for concern. However, a recent large meta-analysis found that stimulants can be used in youth with ADHD without increasing SUD later in life[7]; other studies point to benefits of stimulants in treating CD[8]. Yet, no studies have specifically examined stimulant safety in the context of SUD risk status in humans. Thus, a question of major clinical import remains: can stimulants can be used safely in youth with ADHD and high risk for SUD, or should they be withheld due concerns about increased risk for later SUD?

Functional magnetic resonance imaging (fMRI) offers an opportunity to examine the effects of stimulant medications on the biology of SUD risk in youth with ADHD prior to exposure to drugs of abuse[9]. Emerging findings implicate behavioral disinhibition, heightened sensitivity to reward[10], and decreased connectivity between the behavioral control and reward systems[11-13] in mediating SUD risk. In particular, reduced activation in the reward system in preparation of effort, but increased activation following reward receipt, have been linked to problematic drug use[14,15] - suggesting that SUD risk is characterized by blunted motivation and cognitive effort, but enhanced hedonic properties of rewards. Of note, recent findings indicate that purported neurobiological manifestations of SUD risk may precede the appearance of clinical manifestations[9]. Yet there are only a few studies reporting on activation changes after administration of stimulants, with discordant findings; for instance Rubia et al. (2009)[16] showed that MPH decreased baseline hyperactvation in OFC in ADHD while Minuzo et al. (2013)[17] reported that MPH increased baseline hypoactvation in nucleus accumbens (NAcc) for ADHD vs controls. Yet, while subjects in these studies had ADHD, they did not necessarily have increased risk for SUD, and the findings were not examined in relation to relative risk for SUD. Importantly, preliminary data from our group suggest that youth with ADHD at high risk (HR) and low risk (LR) for SUD differ from controls in relation to reward processing, as demonstrated by prediction error outcomes on behavioral tasks, as well as activation in the reward system on fMRI. These findings highlight the importance of specifically studying the effects of stimulant medication in youth with ADHD and HR for SUD in contrast with those at LR for SUD. Currently, there are no studies which use fMRI to examine youth at HR vs. LR before and after stimulant treatment. This design would be highly informative for assessing effects of stimulants on the biology underlying SUD risk.

We propose to study the effects of 3 weeks of treatment with mixed amphetamine salts extended release (MAS-XR) on the brain reward system in youth with ADHD only (LR) vs. ADHD + CD or severe ODD (HR). We will study 36 youth naïve to stimulant treatment and drugs of abuse (18 per risk group) ages 7– 12 years. LR and HR subjects will be assessed with clinical and neuropsychological measures and will be subjected to fMRI scans twice – before and after 3 weeks of treatment with MAS-XR. The fMRI scans will be conducted while participants perform the Anticipation, Reward, Conflict (ACR) task developed by our group, which has a unique component of unexpected non-reward[18]. Combining prediction error analyses with purported activation differences on this particular component of the ACR will offer a novel approach to assess differences between youth at different risk levels for SUD. Importantly, our event-related design will distinguish increased effort and associated anticipatory activation (positive effects) from increased hedonics of reward (a potentially deleterious effect).

Aim 1 (Primary). To compare the effect of MAS-XR on activation in the brain reward system in LR vs. HR participants with ADHD. Hypotheses: 1a) Based on our preliminary data the HR group will show greater baseline activation than the LR group during the ACR task in the insula, putamen, and anterior cingulate gyrus (ACC); 1b) Based on prior findings of stimulant effects on baseline hyperactivation in ADHD[16], we hypothesize that MAS-XR will reduce the activation in the brain reward system for both groups, with greater magnitude of change in HR youth. Given discordant reports in the literature[16-28], it is possible that MAS-XR will increase the baseline activation in both groups or may increase the activation in one group but not the other.

Aim 2 (Exploratory). We will examine the relationship between behavioral measures and changes in activation in the reward system. We hypothesize that changes on behavioral measures will correlate with changes in activation during the Expected Reward and Unexpected Non-Reward components of the ACR task. We specifically examine: a) positive and negative prediction error measures computed from the behavioral data the ACR task; b) measures of sensitivity to reward and punishment assessed by the subscales from the AS; and c) positive and negative urgency assessed by the UPPS Behavioral Impulsivity Scale.

A. BACKGROUND AND RATIONALE. Vulnerability to substance use disorder (SUD) has been conceptualized as an imbalance between the functions of the brain reward and behavioral inhibition systems[29]. Drug-seeking behavior is linked to the highly rewarding properties of addictive substances, which produce a preference to drugs over alternative naturally occurring rewards, so drug-associated stimuli acquire heightened ability to motivate behaviors. An important recent review concludes that adolescents with attention-deficit/ hyperactivity disorder (ADHD) and disruptive behavior disorders (i.e., oppositional defiant disorder (ODD) or conduct disorder (CD)) exhibit exaggerated sensitivity to rewards in the context of a persistent pattern of behavioral disinhibition[10], and therefore are at heightened risk for SUD. Stimulant medications - the accepted first-line treatment for ADHD - have known abuse potential; moreover, there are concerns about possible sensitizing effects of stimulants on the function and development of the brain reward system. Findings from multiple preclinical studies demonstrate the potential of addictive drugs to alter brain organization in networks involved in the processing of incentive motivation and reward[30-38], and show that neuroadaptations that accompany the development of addiction render the brain reward system hypersensitive ("sensitized") to drugs and drug-associated stimuli[39]. Moreover, animal studies have shown that stimulants enhance drug-seeking/self-administration, whereas non-stimulants diminish those behaviors[6,40]. Similarly, human studies have shown robust effects of stimulants on behavior[41,42] and differential effects of methylphenidate (MPH) vs. atomoxetine (ATX) on brain activation in the context of reward[43].

Despite the above concerns, naturalistic studies have failed to consistently document an association between stimulant treatment and SUD risk - some have shown protective associations[44-46], others predisposing associations[47-49]; and others no association[50-52]. Though it is tempting to conclude that there is little risk of SUD due to stimulant treatment, there is good reason to not summarily accept this conclusion. First, most existing studies have sample sizes of ~100 participants; this is insufficient to examine the association between stimulant treatment and SUD, which occurs at relatively low frequency even in high risk (HR) samples[53]. Second, longitudinal studies tend to under-recruit HR individuals – for instance the MTA sample had low rates of comorbid CD (e.g. 8%) compared to the 20-25% figure reported by others[54]. Third, longitudinal studies cannot randomly assign subjects to long-term medication vs. non-medication treatment due to ethical considerations, and there is inconsistent duration of exposure to medication and dose[7]. Fourth, naturalistic studies which pair clinical measures with imaging to assess the impact of treatment on the brain do not align the timelines for assessment and imaging with treatment – which means that they cannot specifically assess the impact of treatment. Most importantly, no study has examined the possible differential effects of stimulant treatment in youth with ADHD at relatively HR and low risk (LR) for SUD. This is problematic, because treatment might increase risk only in the subgroup of children who might be especially vulnerable.

Yet, even if one accepts the importance of conducting a study of stimulant exposure and SUD risk, the question remains as to how to define risk and how to best measure it. While there is relative convergence regarding the importance of "reward sensitivity" and "sensitization to reward" as proxies of SUD risk, there is considerable disagreement about how to measure these constructs. A question of particular importance is whether to prioritize the study of behavioral or brain-based measures in relation to SUD risk. Of note, Robinson and Berridge[6] argue that behavioral indices of sensitization are important only as secondary measures, to illustrate the consequences of underlying neuroadaptive processes linked to SUD. Other recent research has shown that imaging biomarkers and clinical factors may have different roles as predictors of treatment outcome[55-57]. Together, this evidence suggests that brain-based measures should be prioritized. Most importantly, it is thought that underlying physiological abnormalities can be indexed before the full development of the clinical phenotype[9], meaning that these fMRI-derived biomarkers might be more sensitive to determining risk (i.e. before SUD onset). Thus, to best understand the neurobiological underpinnings of SUD risk, it is essential to study the effects of exposure to abusable substances on the brain reward system in youth who are naïve to such exposure, and examining possible differential effects in youth at relatively HR vs. LR for SUD.

The examination of reward processing in ADHD has so far produced inconsistent results regarding which brain regions are activated by different reward tasks, and also the direction of activation in ADHD compared to controls. A number of studies have shown activation in NAcc during reward anticipation[21,22] and reward outcome[23,24] ; other regions have been indexed by reward outcome, including ACC[25,26], orbitofrontal cortex (OFC)[27,28], and insula[18]. Several small studies have reported that ADHD is associated with under-activation in al striatum (VS) and ventromedial prefrontal cortex (vmPFC)[19], and negative correlations of activation with vioral measures of impulsivity[58]. In contrast, a recent larger study in adolescents and young adults with found hyper-activation in VS[20]. Of note, reports on activation changes in the brain reward system after

administration of MPH have shown discordant findings; for instance Rubia et al. (2009)[16] showed that MPH decreased baseline hyperactvation in OFC in ADHD while Minuzo et al. (2013)[17] reported that MPH increased baseline hypoactvation in NAcc for ADHD vs controls. Most importantly, none of these reports have specifically examined subgroups of individuals with ADHD at HR vs LR for SUD, with the exception of one study from our group that showed higher activation in HR vs LR participants in the caudate and insula[18]. In summary, the existing literature fails to demonstrate any consistent patterns of activation differences; individuals with ADHD may exhibit either higher or lower activation in a widely distributed set of brain regions, and the findings may differ in relation to reward anticipation or outcome. Yet, existing studies have not separately examined individuals with ADHD at HR and LR for SUD.

Summary. This study of drug-naïve youth at LR and HR for SUD studied pre- and post-treatment with amphetamine stimulants would provide important preliminary data for a larger scale investigation of reward-related risk and protective effects of stimulants. fMRI will be used to determine whether brief treatment with stimulants yields differential effects on activation in the brain reward system in youth at HR vs. LR for SUD. Additionally, the degree to which changes in brain activation are linked to measures of ADHD and ODD/CD symptoms and reward sensitivity pre- and post-treatment will provide important information regarding the functional consequences of treatment. This proposal builds on two important and innovative characteristics 1) a strong translational paradigm; and 2) imaging techniques capable of quantifying functions in distributed neural circuits to index imaging biomarkers as indicators of treatment outcome. The goals of the proposed research are in concert with NIDA priorities which “encourage studies…to explore the relationship(s) between neural circuitry and treatment and prevention effects, and in particular, how behavioral targets might be affected by treatment and prevention interventions, and how that information might be used to improve targeted treatment and prevention intervention development, that translate to reduced morbidity and mortality.”

B. INNOVATION The most innovative aspect of this proposal is its use of a translational design to investigate a clinical question of considerable importance that cannot be answered using a more traditional longitudinal approach. The decision to conduct a neuroimaging treatment trial of MAS-XR in drug-naïve LR vs. HR youth with ADHD builds directly from findings in animal and human studies suggesting dysfunction in neural circuits regulating reward processing, the observation that stimulants may be associated with potentially adverse behavioral outcomes (i.e. increased drug self-administration[6] and higher relapse rates in adults with ADHD receiving stimulants[42]), and the recently articulated imperative to prioritize the study of biomarker predictors of risk. This would be the first study to examine the influence of stimulant treatment on the brain reward system in drug-naïve children at LR vs. HR for SUD, and thereby assess the neurophysiological basis of SUD risk in these populations. Further, it will use a validated fMRI task (i.e., Anticipation, Conflict Reward (ACR)[18]), which is developmentally sensitive and uses a novel approach to model reward mechanisms, including specific task components to measure the potentially divergent effects of reward anticipation and outcome. We will further examine changes in brain activation in relation to clinical symptoms and validated measures of reward sensitivity obtained outside the scanner, which will allow us to more extensively determine the effects of stimulant treatment on reward processing in context of clinical features. No study to date has explored changes in the activation of the reward system in drug-naïve children with ADHD subdivided into those with relatively LR and HR for later SUD, and related these changes in activation to behavioral/neuropsychological measures.

C. APPROACH.

C.1. Overview. The objectives of this study are to examine the effects of treatment with mixed amphetamine salts extended release (MAS-XR) on reward processing in youth with ADHD at HR and LR for SUD, and to delineate risk in relation to underlying neurobiological and clinical features. We will recruit 48 youth ages 7-12 with ADHD+CD or severe ODD and treat 42 of these with MAS-XR for 3 weeks. We estimate a dropout rate of ~15%, and expect 36 youth (18 per risk group) to complete treatment and 2 successful scans. Activation changes from baseline to end of treatment (EOT) in components of the reward system (e.g. VS, OFC, insula) will be assessed via fMRI. Ratings of ADHD symptoms will be obtained weekly; secondary neuropsychological and clinical measures of SUD risk will be obtained at baseline and EOT.

Successful completion of this study will illustrate the different effects of stimulant treatment (e.g. MAS-XR) on reward processing and activation during fMRI in youth with ADHD at HR vs. LR for SUD. We will make nces regarding risk for substance abuse based on the presence or absence of differential effects of ment on reward-related activation in relation to SUD risk status. If treatment produces similar changes in ward system in participants at LR and HR, there should be no concern about increased risk for SUD with

treatment. If treatment produces different activation profiles, this would raise questions about the suitability of this treatment in relation to SUD risk. Either way, the findings will inform a subsequent larger scale clinical translational study to more accurately determine the effects of stimulant treatment on SUD risk.

C.2. Rationale for the Project Design

C.2.1. Rationale for Recruiting Children Ages 7-12. There are several advantages to working with 7-12 year olds with ADHD. First, studying the effects of stimulants in young, drug-naïve youth reduces the risk of both naturalistic exposure to drugs of abuse and stimulant treatment of ADHD (both of which are exclusionary). Further, our experience with fMRI studies in youth with ADHD suggests that by age 8 approximately 90% of participants can successfully complete both mock and actual scans. Age-related differences in the BOLD signal will be used as a covariate.

C.2.2. Rationale for Risk Group Definition. Studying LR vs. HR children will allow us to examine the effects of treatment on activation in the brain reward system as a function of risk status and determine whether MAS-XR may impact the reward system similarly or uniquely in HR vs. LR youth. Childhood ADHD has been associated with increased rates of drug abuse in adolescence; however, comorbid CD and severe ODD, which frequently co-occur with childhood ADHD, account for most of this association[1]. Therefore, children who have ADHD and CD or severe ODD (ODD + 2 symptoms of CD) will constitute the HR group. We will not require overt aggression, as this co-varies with CD and severe ODD. We considered requiring both FH and CD/severe ODD to define the HR group, but this would limit feasibility of recruitment. Moreover, CD has been found to be a better independent predictor of later substance abuse than FH of SUD in youth with ADHD[59]. Finally, choosing CD/severe ODD rather than FH to define the HR group offers an important clinical advantage, as stimulants are often used to treat ODD/CD symptoms in youth with ADHD[8]. Because the LR group cannot have + FH of SUD, we will exclude FH in first degree relatives in both the LR and HR groups (so the groups are balanced). A review of our MACRO sample shows that out of 90 youth with ADHD, 53 (57%) had comorbid ODD with no FH of SUD, which indicates that we will be able to recruit a sufficient number of HR youth for this study.

C.2.3. Rationale for the use of MAS vs. MPH. All stimulants (e.g. MPH, MAS, cocaine) activate both the sympathetic and central nervous systems to heighten arousal, increase behavioral activation, and, when delivered rapidly to the brain, create a long lasting state of euphoria[60]. While similar, these effects differ between different classes of stimulants – e.g., existing evidence suggests that MPH-induced changes in brain dopamine and its metabolites are consistent with changes induced by other uptake blockers; however the magnitude of the dose-dependent increase in both the dopamine and norepinephrine responses for behaviorally comparable doses are considerably less than with amphetamine[61]. Therefore, we selected to use MAS for the current proposal due to: 1) stronger effects on brain chemistry that may be closer to the effects of drugs of abuse, and 2) potential use of AMP as replacement therapy in the treatment of cocaine abuse[62].

C.2.4. Rationale for the Treatment Design. We propose an open label study of MAS-XR because the contrasts of interest are between the two SUD risk groups, and placebo is not needed. Available reports show BOLD changes with single dose stimulant challenge[16,63] as well as different lengths of treatment[64,64,65], with some reporting activation changes after 3 weeks of treatment[66]. Therefore we expect that 3 weeks is a sufficient amount of time to show changes on fMRI; it is also not too long to substantially increase cost and risk for dropout. In our prior experience with MPH/ATX comparison trials, the dropout rate was 18% for a 4-month protocol and 10% for a 6-week protocol. Ideally we might have included a control group to assess practice effects, but that would be prohibitive for the scope and budget for this proposal. Data from 4 subjects who did 2 scans with the ACR task without interventions showed no appreciable practice effects.

C.2.5. Rationale for Use of the Anticipation, Conflict, Reward (ACR) task. The fMRI task to be used in this protocol (ACR) was developed by Dr. Jin Fan (co-I) and piloted by our group. The task has several important features: 1) it is developmentally appropriate, and the value of using child-friendly designs to help keep children engaged has been amply recognized[67]; 2) it balances task length and the requisite number of different events (e.g., cues, flankers, reward outcomes), thus decreasing burden and maximizing task completion; 3) it has a novel unexpected non-reward component that can be used to conduct exploratory analyses of reward processing in relation to negative outcomes (i.e., negative prediction error); and 4) it has been shown to successfully index changes in activation in the brain reward system in relation to stimulant administration[63].

Feasibility of Study Design (includes preliminary studies).

. Qualifications. The team has an extensive record of research on the neurobiology and pharmacotherapy

of ADHD, as well as expertise in the use of fMRI to examine activation in the reward system in youth with ADHD and varying SUD risk. The consultants are acknowledged experts in imaging substance abuse risk.

C.3.2. Capacity to Recruit the Sample. Dr. Newcorn's team has an established record of recruiting youth with ADHD who are scanned pre- and post-treatment, and has published one of the very few treatment studies in ADHD directly comparing MPH and ATX using fMRI[59]. We have also successfully recruited drug-naïve youth with ADHD at HR and LR for SUD.

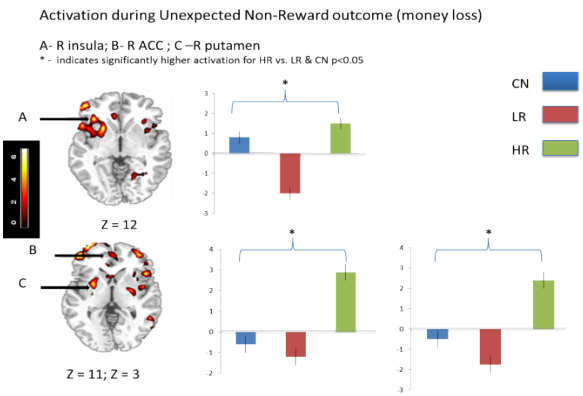

Figure 1.

C.3.3. Preliminary Studies. Our publications show that the ACR task can successfully recruit regions within reward network during reward outcomes and that reward-related activation is elevated in youth at HR for SUD[18]. We have also successfully treated and scanned youth with ADHD treated with MPH vs. ATX[68]. New data show demonstrable higher activation in HR vs LR/controls in insula, ACC and putamen during Unexpected Non-reward outcome of the ACR (Figure 1).

C.4. Methods and Procedures. C.4.1. Sample**.** We will recruit 48 prospective subjects and randomize 42 who meet inclusion/exclusion criteria and complete the baseline fMRI scan to treatment with MAS-XR (21 per group). We budget for ~15% dropout per group leaving a total of 18 per group with completed assessments and scans.

C.4.2. Inclusion criteria: 1) General: pre-pubertal (e.g. Tanner stage 1 or 2), age 7-12 inclusive, signed consent/assent, parent communicates sufficiently in English; 2) ADHD: ADHD as determined by computerized DISC (C-DISC) parent interview[69], ADHD-Rating Scale-5 total score (interview with parent)[70] and SNAP[71] ADHD total score (teacher rating) of 1.5 SD ≥ age/sex norms; 3) CD or severe ODD: CD or ODD + 2 symptoms of CD on C-DISC; SNAP ODD/CD subscale (parent and teacher) 1.5 SD ≥ age/sex norms. Exclusion criteria: 1) major neurological/medical illness; 2) history of head injury; 3) fetal exposure to alcohol/drugs; 4) diagnosis of major psychiatric disorder (e.g., schizophrenia, bipolar disorder, major depression, generalized anxiety, social phobia, Tourette's Disorder, PTSD, autism spectrum disorder); 5) current suicidal ideation or past history of suicide attempt; 6) Wechsler Abbreviated Scale of Intelligence (WASI)[72] score <75; 7) prior or current treatment with stimulants (prior or current treatment with non-stimulants is permitted, but participants must be off medication for 2 weeks at baseline); 8) current or past alcohol/drug use (DISC interview; urine toxicology); 9) psychological or medical condition which precludes being in the scanner (e.g., claustrophobia, morbid obesity); 10) metal in the body that cannot be removed; 11) visual disturbances that may impair task performance; 12) precocious puberty (e.g. Tanner stage >2).

C.4.3 Study Periods

Study Period I: Screening/baseline (Visits 1–2). The 1st and 2nd visits both involve assessment; the 2nd visit also includes the baseline fMRI scan. Subjects will have a "mock scan" at the 1st visit, following established guidelines[76]. We anticipate that the assessment procedures can be completed in 2 study visits within 14 days. The screening period can be lengthened to accommodate washout of a non-stimulant drug if this is required.

Study Period II: 2 Week Treatment Block (Days 0 to 21)**.** Subjects will receive open label treatment with MAS-XR for 3 weeks. Medication will be titrated using a fixed dose approach, with doses that mimic those used in clinical practice. The two assigned doses are 0.25 mg/kg and 0.5 mg/kg, with an option to increase to 1.0 mg/kg if needed. At study completion, participants will complete the post-treatment fMRI scan and all clinical measures. There will be 2 visits during this period - one after 1 week of treatment and one at 3 weeks (EOT). There will be a phone visit at the end of the second treatment week, though subjects can be seen if necessary.

C.4.4. Study medication and medication administration. Subjects treated with non-stimulants will be required to be off medication for 2 weeks prior to the scan. We will purchase MAS–XR, an extended release generic amphetamine formulation. Subjects will begin at 0.25 mg/kg and increase to 0.5 mg/kg after one week. This dose can be reached (within ~5 mg) using 2 capsules of commercially available doses. Those who cannot increase the dose due to AEs will be allowed to maintain their dose and be evaluated for a dose increase after 2 weeks. Subjects who experience difficulty with symptom control can titrate to a higher dose if need be (maximum 1 mg/kg). Subjects who increase their dose and experience AEs will be allowed to lower their dose. Subjects will receive MAS–XR on the day of the second scan approximately 6-8hrs before scan.

C.4.5. Measurement and Management of Adverse Effects (AEs). AE ratings will be collected at baseline and each medication visit, using open-ended reporting and the Barkley stimulant side effect scale[73]. We also monitor for changes in pulse and blood pressure, and suicidal behavior (see below). All AEs are logged and reported to the IRB; profiles of AEs are reviewed by the DSMB annually. We have conducted similar trials using stimulants for years and have never had to modify the protocol due to AEs.

C.4.6. Data Management. Demographic and clinical data will be recorded on paper forms, de-identified, and translated to a Microsoft access database. MRI data will be uploaded to the Mount Sinai High Performance Computing system, identified by number only; imaging data will be backed up to a hard drive.

C.5. Description of Tests and Procedures

C.5.1 Measures to Characterize the Sample. KSADS or C-DISC)[69] *(~45-90 minutes*). The C-DISC and KSADS assesses current and past psychopathology according to DSM criteria. Dimensions of psychopathology. Child Behavior Checklist (CBCL)[74] *(~30 minutes*). The CBCL is a validated and well-established broad-band parent-report scale, which will be used to characterize the sample. ADHD Rating Scale-5 (ADHD-RS). Investigator interview with parent *(~15-20 minutes*); teacher report[70]. SNAP ODD/CD (parent/teacher)[71] *(~5-10 minutes*); The SNAP is a comprehensive 90 item rating scale for ADHD and ODD/CD. It will be used to operationalize inclusion criteria for the ADHD children and serve as a measure of treatment response. To minimize burden we will use only the ODD and CD items. Symptom Severity: Clinical Global Impressions - Severity Scale (CGI-S)[75] *(~2 – 5 minutes*). The CGI is a clinician rated 7-point scale completed by the clinician based on review of all available information. The companion CGI-Improvement scale (CGI-I) will be used to rate improvement from baseline to end of treatment. Wechsler Abbreviated Scale of Intelligence for Children (WASI)[72] *(~20 minutes*). Substance Use. Urine toxicology will be obtained at baseline to ensure that no substances of abuse are being used by the child. Prenatal exposure to alcohol/drugs, assessed via the Pregnancy and Birth Questionnaire[76] (completed by the parent) *(~5 min*). Family History of psychiatric disorders and SUD. Family History Assessment Module (FHAM)[77] (*~25 min*) is a semi-structured diagnostic interview conducted with the parent. Medical Status. We obtain height, weight, hand dominance[78], sexual development assessed by Tanner self-report scale for puberty[79] and a physical examination at baseline. We screen for individual and family cardiovascular risk, and obtain additional consultation as necessary, including ECG, to document of safety for study participation.

C.5.2.Tolerability: **ASSERS [**Barkley Stimulant Side Effect Rating Scale[73]] *(~5 minutes).* Columbia Suicide Severity Rating Scale (C-SSRS)[80] *(~5 minutes)*. Heart rate and BP *(~5 minutes)* and open ended report of AEs and concomitant medications *(~2-5 minutes)* will be obtained at baseline and each treatment visit (weeks 1–6).

C.5.3 Secondary (Behavioral) Measures: Behavioral Inhibition/Activation Scale (BIS/BAS)[81] *(~10–15 minutes)* is a validated 20-item scale that has been shown to correlate with activation in reward circuits[82]. Kirby Delay Discounting Task[83] *(~10–15 minutes)* is a validated test which assesses temporal (delay) discounting; the temporal discount parameter has been shown to correlate with the activation in the reward brain circuitry in adolescents[84]. UPPS Impulsive Behavior Scale consists of 45 items using a 4-point Likert scale and has 4 subscales: Urgency, Lack of Premeditation and Perseverance and Sensation Seeking[785].

C.6. Study timeline

Timeline of study recruitment	**Year 1**	**Year 2**	**Total**
Subjects Screened	N = 24	N = 24	N=48
Subjects Randomized	N = 21	N = 21	N=42
Subjects Completed 2 scans	N = 18	N = 18	N=36

C.7. Neuroimaging Methods

C.7.1. Neuroimaging Procedures. Equipment. The Siemens 3T MAGNETOM Skyra is an FDA approved 3 Tesla human MRI scanner. It has a short and open bore (173 cm system length with 70 cm Open Bore Design). The magnet is equipped with actively shielded echo-planar capable Siemens (SONATA) whole-body gradient coils and Siemens CASCADE gradient amplifiers. A Siemens 32ch head coil is also available for improved signal-to-noise ratio in the cortical area, and increased parallel imaging capability.

C.7.2. Task paradigms. The ACR is an event-related task that provides 3 temporally distinct probes of reward anticipation, conflict resolution, and reward outcome. It consists of four 32-trial blocks, each 6 minutes long. There are 2 cue types (reward/non-reward) followed by congruent/incongruent flankers: both cue and flanker trials are counterbalanced and are fully orthogonal. Participants are required to respond as quickly as they can to the direction of the central arrowhead while ignoring the flankers. Correct responses in trials beginning with reward cues yield $1 reward. Incorrect or slow responses are followed by a $1 loss. The ACR task provides only 25% money wins and introduces reward violation (unexpected non reward) in 25% of the trials, which results in strongly engagement of the insula, ACC and also putamen predominantly during reward outcomes.

C.8. Data Analysis

C.8.1. First level (within-subject) analyses will be conducted for each participant with a general linear model (GLM) to quantify the relationship between the observed event-related BOLD signals and regressors encoding expected trial-specific responses. The design matrix will be comprised of 12 regressors: 2 for cue (reward vs. non-reward) x 2 for target type (congruent or incongruent flankers) x 3 for outcome-related effects (reward, non-reward, punishment). There are 4 outcome contrasts of interest: reward following reward cue, non-reward following reward cue, non-reward following non-reward cue, or punishment for an incorrect/missing response.

C.8.2. Group-level Statistical Analysis. Descriptive statistics (e.g., means, standard deviations (SD), etc.) for all variables of interest will be computed and compared by Student t test for continuous variables or Chi-square test for categorical variables. Group statistical analyses of the imaging data will be performed using a GLM from SPM. The GLM is written as Y=XB+E, where Y is a matrix with a series of multivariate measurements, X is a design matrix, B is a matrix containing parameters that are usually to be estimated and E is a matrix containing errors or noise. The errors are usually assumed to follow a multivariate normal distribution[86,87].

Primary Aim. Hypotheses 1a) HR will show greater activation than LR at baseline will be tested via F-test of the voxel-based whole brain activation with one-way ANCOVA with group (HR, LR) as the between-subjects factor; age, sex, and IQ are nuisance covariates.: 1b) MAS-XR treatment will reduce activation in both groups, with greater magnitude of change in HR youth, will be tested via F-tests with ANCOVA of the voxel-based whole brain activation controlling for time (baseline, post-treatment) with groups (HR, LR) with age, sex, IQ and medication dose as covariates. We will use t-tests to examine 1) differences in activation at baseline and 2) activation differences at end of treatment between HR and LR in specific ROIs. The voxel-based Z statistic images will be thresholded using clusters determined by Z>2.3 and a cluster corrected significance threshold of p<0.05.

Exploratory Aim. We will conduct correlation analyses between pre to post- treatment measures of activation in the reward system and scores on the behavioral measures collected outside the scanner (i.e., Kirby, BIS/BAS, UPPS) to examine the direction and magnitude of correlations between brain function and behavior.

C.8.4. Power analyses. The main power considerations for the primary aim are related to the ability to detect differences in activation between the two groups pre- to post treatment. We estimated power using Monte Carlo simulations (10,000 draws per model), with α = 0.05, for all models. With a between subjects factor (2-levels; LR, HR) and *4* covariates (age, sex, IQ, *dose level*), we were able to recover large effects sizes (f = .80-1.0) for the between group factor with 40 ADHD subjects, which corresponds to approximately a .8-1 difference in activation. For the exploratory aim, we used regression models with the behavioral measures, the same 4 covariates, using the baseline level of each behavioral measure to control for time effects and activation as the dependent variable. In the simulations, we were able to recover effect sizes of *d* =.2-3 with 4-5 independent nuisance covariates (age, sex, IQ, does), and baseline covariates with a correlation of .35 in the model.

C.8.5. Expected outcomes/interpretation of findings. Reduced reward-related activation after treatment with MAS-XR would suggest that the drug may reduce SUD risk by decreasing hypersensitivity to reward; this finding should be amplified by ratings and test measures of reward sensitivity and related constructs obtained outside the scanner. The degree of correlation between brain activation and behavioral measures will inform as to which behavioral scales are most appropriate to use in our planned R01.

C.8.6. Potential problems. It is possible that treatment with MAS-XR will yield activation changes in the opposite direction from what was hypothesized – i.e., increased rather than decreased activation in the HR . Although against the hypothesis advanced here, this finding would be of considerable interest, as it suggest that stimulants might be associated with increased rather than decreased risk of SUD in youth for SUD. This would then become the subject of a subsequent large scale study.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Brain Indices of Stimulant Treatment in Drug-Naive Youth at Risk for Substance Use Disorder	Yes

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Brain Indices of Stimulant Treatment in Drug-Naive Youth at Risk for Substance Use Disorder

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	○ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	○ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	○ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- ADHD

2.2. Eligibility Criteria

1) General: pre-pubertal (e.g. Tanner stage 1 or 2), age 7-12 inclusive, signed consent/assent, parent communicates sufficiently in English; 2) ADHD: ADHD as determined by computerized DISC (C-DISC) parent interview, ADHD-Rating Scale-5 total score (interview with parent) and SNAP ADHD total score (teacher rating) of 1.5 SD > age/sex norms; 3) CD or severe ODD: CD or ODD + 2 symptoms of CD on KSADS; SNAP ODD/CD subscale (parent and teacher) 1.5 SD > age/sex norms. Exclusion criteria: 1) major neurological/medical illness; 2) history of head injury; 3) fetal exposure to alcohol/drugs; 4) diagnosis of major psychiatric disorder (e.g., schizophrenia, bipolar disorder, major depression, generalized anxiety, social phobia, Tourette's Disorder, PTSD, autism spectrum disorder); 5) current suicidal ideation or past history of suicide attempt; 6) Wechsler Abbreviated Scale of Intelligence (WASI) score <75; 7) prior or current treatment with stimulants (prior or current treatment with non-stimulants is permitted, but participants must be off medication for 2 weeks at baseline); 8) current or past alcohol/drug use (DISC interview; urine toxicology); 9) psychological or medical condition which precludes being in the scanner (e.g., claustrophobia, morbid obesity); 10) metal in the body that cannot be removed; 11) visual disturbances that may impair task performance; 12) precocious puberty (e.g. Tanner stage >2).

2.3. Age Limits	Min Age: 7 Years	Max Age: 12 Years
2.4. Inclusion of Women, Minorities, and Children	R21_Inclusion of women and minorities-March.pdf	
2.5. Recruitment and Retention Plan	Subject Recruitment and Retention.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	Study timeline.pdf	
2.8. Enrollment of First Subject	07/01/2020	Anticipated

Inclusion of Women, Minorities, and Children

Inclusion of Women

There are no gender restrictions for this study; we will recruit both males and females. Due to the gender distribution between males and females with ADHD diagnosis in youth, we expect a somewhat larger number of males (estimate between 3 males to every 1 or 2 females). We expect the gender ratio to more heavily favor males in the group with ADHD + CD/severe/ODD, and to be more balanced in the ADHD only group. The control group will be recruited to reflect the age and sex characteristics of the clinical sample.

The sex ratio of the parents who will provide assessment information about their children (and also their families) will be 75 - 90% female. Although ~50% of our cases have a father or father figure who is involved, and although encourage participation from both parents (especially during the baseline and end of treatment assessments), we most often only see the mother. Ongoing medication visits are almost always conducted with the mother and child. In rare circumstance, a father or grandfather will be the primary contact and informant, although in those instances we also solicit information from the mother.

Inclusion of Minorities

Because we are located in a large urban area, there is ample minority representation. Findings from previous research studies conducted by our team indicate that the ethnicity of our participants is approximately 40% Hispanic, 30% African-American, 20% Caucasian and 10% of Asian or mixed ancestry. It is expected that a similar representation will be seen in the proposed study. The sample is also likely to vary with regard to socioeconomic status (SES). Using the Hollingshead's scale (Hollingshead, 1975) for rating SES, the median SES in our samples is 4, though participants span the full range from 1 - 6. This SES distribution closely matches the ethnic and SES make-up of the region in New York City where the research is being conducted.

Inclusion of Children

The participants in this study will be children and pre-pubescent adolescents. Our specific age range (7-12) was guided by our team's experience conducting fMRI studies in youth with ADHD and risk for substance abuse. By adolescence, there is a growing risk of substance abuse and potential for pregnancy among females with behavioral problems (both exclusory condition) and thus a significantly increased risk of attrition at screening.

Subject Recruitment and Retention. Participants in the two groups will be recruited from multiple sources, including the Mount Sinai Child and Adolescent Psychiatry Outpatient clinics (see letter from Dr. Liu), community-based programs (see letters from Mrs. White,), the Mount Sinai General Pediatric Clinic, and the Center for Addictive Disorders (see letter from Dr. Hurd).

Dr. Newcorn's previous experience with imaging adolescents with ADHD indicates that, by using telephone pre-screening, it is possible to limit the number of enrolled subjects who are "screen failures" to 15% - either because they don't meet the study criteria or because they cannot perform the fMRI scans. We have not had difficulty recruiting normal controls for neuroimaging protocols; we anticipate the need to recruit 35 to obtain a final n of 30 controls with completed assessments and an fMRI scan. *All together, we anticipate pre-screening a total of ~60 youth with ADHD in order to enroll 48 at-risk subjects. We have built in an estimated 15% attrition rate in the treatment trial, mainly due to poor tolerability or lack of response. This number is based on our current experience in fMRI treatment studies in youth with ADHD, including a randomized parallel group fMRI treatment study of atomoxetine and methylphenidate.* However, we will over-recruit if we do not meet our expected end of treatment numbers. We expect that given our history of successful recruitment of children with ADHD and paid advertising, we should be able to reach the final number of 36 participants at risk (i.e. 18 per cell) with full clinical and fMRI data at baseline and post-treatment. We anticipate being able to evaluate 3 new participants per month and randomize 2 subjects per month.

A variety of methods are used to enhance recruitment and retention. Families are compensated for their time in participating in the research. All subjects receive a comprehensive evaluation, including a variety of clinical and neuropsychological assessment measures, which can be useful for school placement or obtaining accommodations. They receive treatment with an approved medication for ADHD without risk of randomization to placebo. They will receive case management services during the trial. In case of sub-optimal response or poor tolerability in the trial, they can receive open treatment with a medication of their choice after the trial. And they can often be referred to after-care within our clinical treatment programs.

Study timeline

Timeline of study recruitment	Year 1	Year 2	Total
Subjects Screened	N = 24	N = 24	N=48
Subjects Randomized	N = 21	N = 21	N=42
Subjects Completed 2 scans	N = 18	N = 18	N=36

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	Icahn School of Medicine at Mount Sinai

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ○ Yes ● No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Icahn School of Medicine at Mount Sinai

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	1	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	5	1	4	14
White	3	9	2	3	17
More than One Race	1	4	2	7	14
Total	9	19	5	15	48

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Protection of Human Subjects.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	Data Safety Monitoring Plan Nov 17.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	● Yes ○ No
3.5. Overall structure of the study team	Overall Structure of the Study Team.pdf

5. Potential Risks to the Subjects.

There are several potential risks to participation in these studies. This study involves collection of interview and self-report questionnaires, neuropsychological testing and having a magnetic resonance imaging scan. It also involves administration of medication to youth with ADHD. While fMRI and the ratings are deemed to be minimal risk, any study involving the administration is deemed to be more than minimal risk. ADHD subjects will have potential for benefit by having a thorough structured clinical evaluation, and receiving treatment with an FDA-approved medication. Aspects of the testing protocol may prove beneficial to healthy controls, although the battery is not designed to specifically benefit this group. The potential risks are:

5.1. Clinical trial

There is some risk to participation in the trial, since children and adolescents will receive treatment with MAS-XR which is commercially available FDA - approved treatment for ADHD. Common side effects include: insomnia, loss of appetite, irritability, headache, occasional dysphoria, and tics. Other more serious adverse effects such as palpitations and increased heart rate have been documented.

It is inevitable that in a study such as this, which includes treatment of youth with ADHD, with one subgroup deemed to be at high risk for SUD based on the presence of a comorbid disruptive behavior disorder, there may be problems which require management (emergency or otherwise). For routine management issues of the sort to be expected with this population, we are providing case management. For problems related to medication tolerability or safety, the treatment visit window can be shortened to as little as three days if tolerability at any dose of either medication is poor. For more emergent problems, we will utilize a version of the MTA (Multimodal Treatment Study of Children with ADHD) ASAP (i.e., Adjunct Services, Attrition Prevention) manual[93]. The ASAP manual lays out a procedure for assessing crisis situations, and allows for a pre-determined number of non-directive, supportive counseling sessions to help patients and families respond to crises. To address potential problems from lack of response to the study medications (both are FDA-approved and, in general, are considered to be quite effective for treating ADHD, but some individuals may not respond to or tolerate the rug to which they are randomized), we will offer open treatment after the completion of the randomized trial, using any treatment approach that seems indicated. If none of the above methods are successful in managing the problem, we will encourage subjects to discontinue the trial if it is not in their best interest to remain as participants.

Emergent events need not be related to the trial. One example is real or perceived child abuse, maltreatment or neglect. Current ongoing abuse or neglect is an exclusionary criterion for the study. However, if abuse is suspected after enrollment, we will, as mandatory reporters, make a report to the appropriate agency. Suspicion of abuse will not necessarily be grounds for dismissal from the study (depending on the situation), but confirmed abuse will result in termination from the study.

The other potential risks and discomforts for subjects are, in general, minimal. No discomfort is expected with psychological examinations or clinical interviews.

Additional risks are related to confidentiality of personal information. Every effort is made to protect confidentiality. All individual information obtained will be held strictly confidential. No information that might in any way lead to the identification of the source will be made public. All raw data from the study will be kept in locked files and identified by ID number only; names, addresses, and any other identifying information of study individuals or families will be kept in an entirely separate, locked location. The consent forms will be stored in a separate and secure location from data obtained using the other data collection methods. All study data will be used

for research purposes only and retained at a minimum until the research project is completed. All study personnel will receive Human Subjects and HIPAA training to ensure compliance with IRB and research ethics guidelines. Electronic data will be protected on a secure server behind a firewall and in accordance with HIPAA regulations. All PHIs will be stored on a SQL server with access permitted on the basis of need.

5.2. fMRI study and procedures

We will examine critical SU-relevant domains with a novel and validated tasks that will allow us to provide a neurocognitive profile across our domains of interest that target pathways to SUD. All children will perform the Anticipation, Conflict, Reward (ACR) task; we estimate that the fMRI sessions, including the structural scans required for co-registration, will require about 40 minutes to complete. We will use the MRI facilities of the Mount Sinai Translational and Molecular Imaging Institute. Images will be acquired on a Skyra 3.0 Tesla magnet using a gradient echo T2*weighted echo planar imaging (EPI) (See Approach section) with a blood oxygen level dependent (BOLD) contrast. All MRI procedures combined will require approximately 1 hour of scan time. Based on our experience and feedback from similar populations, the imaging tasks are considered fun and enjoyable, and do not induce distress.

There are very few potential risks to participation. The MRI scan requires the participant to lay still with his/her head in a tunnel-like device. The procedure is painless and not uncomfortable. A small proportion of participants (about 3%) have difficulty tolerating the procedure because of claustrophobia. If a participant becomes upset by the procedure, the study will be terminated. There is no evidence that MRI is in any way harmful or has adverse effects. The Food and Drug Administration (FDA) has set recommendations for exposure in MRI studies and this study satisfies those criteria. Persons not suited for this study include those who have cardiac pacemakers, neural pacemakers, surgical clips in the brain or blood vessels, surgically implanted metal plates, screws or pins, cochlear implants, or metal objects in their body, especially in the eye. Dental fillings do not present a problem. Some subjects find the loudness of the oscillating gradients during image acquisition to be discomforting, but the noise level is below FDA guidelines of 140 dB peak referenced to 20 micropascals. In addition subjects are provided with ear plugs and headphones to reduce the noise.

We manage the risks of having an MRI scan in several ways. We offer practice on the task outside the scanner before the scan, and have the child warm up to the experience of being in the MRI scanner by having a “mock scan” before the actual scan takes place. This provides the child experience with the scanner environment, including lying inside the MRI tube and performing the task, and accommodating to the noise which is typical of this procedure.

There also are potential risks from the tasks, which are in general minimal. The animation used in the ACR task offers neutral images that are unlikely to be upsetting to participants, however, all participants will be shown a subset of comparable stimuli outside the scanner and will be exposed to practice versions of the task they will undergo in the scanner and are provided with the opportunity to withdraw from the study if they find the task aversive.

6. Adequacy of protection against risks.

6.1. Vulnerable subjects:

6.1.1. Children. Children are considered to be vulnerable subjects; therefore, the Mount Sinai Medical Center Certification of Assent procedure will be used. The investigator will explain the protocol to the child in a developmentally appropriate manner. If the child agrees to participate, he/she will be asked about the protocol by an independent individual, who is not related to the child and is not involved in the study (e.g., a clinic nurse, clinician; administrative assistant; or staff from other research groups). This individual will certify in writing that the child indeed

understands the protocol and assents to participation (and that this assent is free of coercion). If assent is not obtained, evaluation will not commence even if the parent consents. In addition, the clinicians and other personnel involved in this study will be trained in the management and interviewing of children.

6.1.2. Financially disadvantaged persons. The study population is expected to include subjects from all financial and social strata. We will not exclude a subject based on financial parameters nor will we ask for a payment for the evaluation. The reimbursement (for baseline assessment and two scans) for subjects' time is enough to cover transportation fees and a lunch at the time of the interview, but is not coercive in that it does not constitute an unreasonably high incentive for participation - even for financially disadvantaged persons.

6.2. Recruitment. Participants and their parents will be clearly told that participation in the present study is voluntary and that they can choose not to participate and still receive treatment in the Mount Sinai clinic or another treatment facility of their choosing. We also aim to reduce the boredom of the fMRI scan by using child-friendly tasks, which appeal to the child's potential interest in doing the scan when they are considering whether or not to participate, and maintain the child's interest in performing the tasks properly during the procedure. Pilot data from other fMRI treatment studies we have conducted in youth with ADHD indicate that we can recruit the requisite number of youngsters for studies using fMRI, and that the majority are interested in participating and would participate again if asked. In addition, very few children who can successfully complete the scan ask not to do the procedure again.

6.2.1. Informed Consent. Participants will be pre-screened prior to the first visit to inform the adolescents and caregivers about the research trial and to identify basic inclusion/exclusion criteria. If participants wish to enroll in the study, consent forms will be sent to the home so the caregivers can review them. Enough time is given for the caregiver to read the consent form and discuss it with a family member or the current care provider, if so desired. Prior to the initiation of study procedures, the consent form is read and explained to the participant and his or her caregiver by the investigator or a delegate. The consent form includes the purpose and description of the study procedures as well as the potential risks and discomforts, cost/reimbursements, compensation for injury, confidentiality, voluntary participation, alternatives to participation, potential termination of participation, financial disclosures of interest, and names of contact persons. Following a review of the consent form, all participants and their caregivers will be queried about distinct aspects of the study, and the time involved in the various procedures, to ensure they were paying attention to the description of the procedures and understood what they heard and read in the consent document. After a thorough description of the research, including the risks and benefits and the alternatives to participation, the parent or caregiver is asked to sign the consent form if they freely consent to the procedures of the study. The caregiver will also sign Health Insurance Portability and Accountability Act (HIPAA) forms, which indicate to the caregiver how information regarding the participant is disclosed. A witness, not associated with the research study team, will meet with the adolescent independently and sign and date the MSSM "Certification of Assent of Minor" form to document that the child freely assented to participate. The MSSM Certification of Assent form is used for ALL children, regardless of age, to document assent was freely given without coercion. The caregiver and the research study delegate obtaining the consent will sign the consent form.

6.2.2. Compensation.

All participant payments are in keeping with IRB approved levels and are generally at the low end of payment practices for similar participation in the US. To reimburse the families for time away from work we will pay compensation for the completion of the fMRI scan in the amount of $50

The average payout for the tasks is ~$20. All in-person interview payments and earnings from the tasks (won and to be paid on the same day) will be paid on the day of the interview either in cash or gift certificate. Depending on IRB requirements, children/youth may receive gift certificates instead of cash, or a combination of cash and gift certificates the day of their visits. We will offer compensation for public transportation in the amount of $20 per visit.

6.3. General Procedures.

6.3.1. Psychological risks**.** The clinical scales and psychometric instruments used in this study are primarily standardized, commonly-used instruments. Many are used in clinical practice but others are more specific to the research setting. Most children experience the testing sessions as fun, although a small proportion may find the tests boring or tedious. The child or the parent may feel discomfort while talking to the clinician about adverse life events and traumatic experiences. The subjects will be explicitly told that they can stop answering questions or terminate the interview at any time. The interviews and the consent procedure will take place in a dedicated room, not in the waiting area, so that subjects would feel less compelled to answer questions or to "behave". When indicated, children who will not feel safe alone will be interviewed together with the parent.

6.3.2 Discovery of previously unreported abuse: This will be discussed immediately with the participant and family and reported as indicated and in accordance with NY State law. Cases will be managed immediately by a board certified child psychiatrist, who is a member of the research team or when indicated, by another care provider. The child will not be discharged until safety is established in accordance with prevailing clinical practice. In cases where safety cannot be established, the child will be taken for further evaluation in the pediatric emergency room.

6.3.3. Suicidal or homicidal ideation revealed during the course of evaluation: A board certified child psychiatrist, who is a member of the research team, will evaluate the child and if necessary, the adolescent will be taken to the emergency room for additional evaluation. Although the PI will assist in this procedure, the primary decision with respect to possible hospitalization will be made by the clinical consultation/liaison team, which conducts the emergency room evaluation, and not by the research team. This will ensure that all decisions regarding management reflect the clinical needs of the participant, and not any considerations in relation to the research.

6.3.4. Discovery of a previously unknown psychiatric disorder during evaluation: If safety is compromised or could potentially be compromised, the information will be reviewed with the family by the Co-PIs or one of the Co-Is. If there is no threat to safety and the newly discovered disorder represents a contraindication to participation (e.g., the discovery of a Major Depressive Disorder with no psychotic features and no suicidality), the parent and the child will be counseled accordingly and encouraged to seek help. If the parent agrees to seek further treatment, a referral for further evaluation will immediately be made. Research participants can often be seen for a reduced fee in the child psychiatry outpatient clinic. A range of other potential sites for clinical follow-up will also be offered. Participants referred to clinical services within Mount Sinai will receive standard-of-care treatment, which may include psychotherapy or medications. Decisions related to possible treatments will be made by the clinician(s) at the outpatient clinic, or other clinical site.

6.3.5. Management of transient anxiety that may be caused by the questionnaires/procedures: This will be managed immediately by the research team, including attempts to better understand the source of the problem, and to provide acute intervention as required. Should any

intervention be made by the research team, the participant/family will not be responsible for payment for this intervention. It is very unlikely that more than one brief session will be needed for the treatment of anxiety caused by the questionnaires, should it occur. However, in the case of pre-existing psychopathology that may make any anxiety which arises more resistant to intervention, the child will either be immediately evaluated by the consultation/liaison team or referred to the Mount Sinai outpatient clinic. Participation in the study will be suspended if this occurs, and not resumed unless and until the child and family agree to continue the research evaluation, and the evaluating clinician agrees that proceeding with the research evaluation is not contraindicated.

6.3.6. Positive urine toxicology: Both parent(s) and child will be informed during the informed consent procedure that a urine toxicology test will be part of the initial evaluation, and that if there is a positive finding, the result of the test will be revealed to both the child and the parent. If this occurs, the PI or other qualified team members (e.g. child psychiatrist, psychologist) will counsel the family and discuss options for further action. Since positive urine toxicology is an exclusionary criterion for study participation, participants who have positive urine toxicology tests will be discontinued from the study.

6.4. Clinical trial.

6.4.1. General Issues. All interviewers will receive thorough and rigorous training on all aspects of interview administration, confidentiality, subject recruitment and acceptable methods of interviewer-subject interaction. All responses will be held confidential, to the extent permitted by law, including from the treatment/court authorities and other family members. Interviewees will be informed that reports or observations of suspected child abuse may require reporting to Child Protective Services and that information about other possible threats to the child (such as suicidality) may need to be reported to parents/guardians. Parents and youth are informed before the start of the interview that any threat of harm to or by a minor child will have to be reported to the parent and that any threat of child abuse or homicidal threat must be reported to the appropriate authorities. Parents will be told of any serious threat or harm to their child. All limits to confidentiality will be explained to all participants and their parents during the consent process. Even though the participants read the consent/assent forms, the specific sections of the consent form addressing these issues will be read to parents and children. Specifically, they will be told that we will protect the participant's confidentiality and that we will not share any personal information collected. Parents will be explicitly informed that they cannot have access to any of the research self-report data, including information collected about their child's substance use or other high risk behaviors, unless their child is in imminent danger and/or it is clinically determined that they need an intervention that requires parental consent.

6.4.2. Medications. The medication to be used in this study is FDA-approved for the treatment of ADHD. While some would argue that stimulants are more effective in both risk groups to be studied, others would argue that non-stimulants might be preferable, either as a general rule or specifically in high risk subjects. As a rule, non-stimulants are considered a more appropriate first choice in youth who are currently abusing drugs, but there are no guidelines about whether to use stimulants or non-stimulants in children with ADHD + comorbid ODD/CD. Many would say that stimulants are more effective and should be used in this population; others might favor non-stimulants. It is clear that there is room for both clinical judgment and the different opinions held by clinicians and parents with regard to medication selection in the treatment of youth with ADHD. However, with specific regard to randomization in this study, stimulant medication is indicated in the subject groups being treated and appropriate to use.

6.4.3. Dose titration. We use an escalating, dose-optimizing approach that incorporates measures of clinical response and tolerability, and is maximally responsive to the clinical needs

of participants. If there is inadequate response and tolerability is excellent the dose will be increased. If response is deemed to be excellent (and tolerability at least good), the dose will be maintained. If an initial excellent response is not maintained, the dose can be increased. Likewise, if the medication is not adequately tolerated, we will either maintain the dose (i.e., allowing additional time to accommodate) or lower the dose. If tolerability improves, we will increase the dose until optimal response is reached (i.e., CGI-S rating of 1 or 2).

6.4.4. Monitoring and managing problems in titration. Children will be monitored closely during the study, with weekly visits during medication titration and treatment. The interval between visits and the schedule of dose changes can be altered if clinically warranted. For example, if there is a problem with tolerability or an adverse event that prevents dose escalation, the pharmacotherapist can maintain or lower the dose. If titration is slowed in order to accommodate to adverse effects, but tolerability is subsequently achieved, the duration of the trial can be extended. In addition, the visit window can be increased or decreased (by 3 - 4 days in either direction) as clinically warranted.

6.4.5. Clinical emergencies: Clinical emergencies are defined as any situation where a subject expresses or shows: 1) potential for harmful behavior (to self or other), such as suicidal ideation or behavior or threat of violence/homicide; 2) serious emotional distress; or 3) impairment of reality testing (e.g., unable to communicate coherently, illogical response, hallucinations). If a subject manifests behaviors that constitute a clinical emergency either during an interview or at another time, the principal investigator and appropriate clinical staff will be contacted immediately and provide a thorough review of the situation. If it is deemed that further or additional interventions are required that cannot be offered by the study, an appropriate referral will be made. This study also uses a procedure called ASAP (Adjunct Services/ Attrition Prevention) utilized in the Multimodal Treatment Study of Children with ADHD[93], which offers two sessions of supportive, non-directive counseling and/or problem solving for patients who experience difficulties in the trial, which require emergent intervention but do not reach the threshold for referral to an outside provider. Often, this procedure helps youth and parents to make a plan during an immediate crisis period, without having to drop out of the trial. However, we will encourage participants to drop out if there are substantive clinical problems of an emergent or time sensitive nature that cannot be addressed within the trial.

6.4.6. Discontinuation from the study: Subjects may withdraw at any time or be withdrawn should contraindications to continued participation develop. Subjects will be terminated early if there is: 1) Intolerance to study drug that cannot be managed by dose reduction; 2) worsening of symptoms which poses serious risks to the subject or others; 3) significant medical or psychiatric complications, even if not related to the study drug.

6.4.7. Poor Adherence: We track medication dispensed, taken and returned at each visit. Subjects who are non-adherent are counseled regarding proper use of the medication. Subjects who are repeatedly non-compliant may be withdrawn from study. In our experience, this rarely is necessary.

6.4.8. Dropouts: Subjects who do not complete at least 3 weeks of randomized medication are considered dropouts. Subjects who prematurely discontinue the trial will be encouraged to complete their fMRI scan.

6.4.9. Clinical Support/Back-up:

As in all our studies, we routinely have clinical back-up available, so that if necessary, a psychiatric consultation can be arranged immediately, especially in cases of suicidal or homicidal concern. All interviewers will be thoroughly trained in appropriate response to reported or otherwise presented clinical issues. Also, during MRI procedures, Drs. Newcorn and

Ivanov (Co-PIs on this protocol) will be available for immediate consultation, if necessary. In cases of suspected abuse, the interviewer will obtain specific information, which will then be transmitted to the Principal Investigators, who will consult and decide what action must be taken. We will also provide all study parents with a list of local mental health/substance abuse services and family support organizations.

We have a well-established protocol for addressing situations that may indicate an issue of clinical concern, or which may pose a threat of harm to either the youth or the parent. If a threat of harm to the child is reported, the parent will be told before leaving the Study Center. If the threat is urgent (e.g., current suicidality or threat of violence), one of the study clinicians may be called directly to intervene. If need be, the family may be referred to the Mount Sinai emergency room. All cases involving past or present threat of harm to a minor child (e.g., suicidality, bullying), even if help has been obtained, are discussed with the parent. In all cases of clinical concern, interviewers must fill out a clinical report before leaving the Study Center and, if the issue is not urgent, must contact the appropriate study administrators within 24 hours of the interview. If there is some additional concern, the interviewer contacts the administrator immediately after the interview. Administrators then contact the study team clinicians, who then call the family directly. In cases of suspected abuse, the Principal Investigator(s) will consult and decide to see what action should be taken. In cases where a participant may become distressed during the interview, they will be offered the opportunity to stop the interview for a while or, if they wish, to complete the interview at another time. If they wish, they can also speak with one of the study administrators and/or clinicians.

Drs. Newcorn and Ivanov (the study Co-PIs) have established relations with the Child Psychiatry Consultation Liaison, the Psychiatric ER and the Child and Adolescent inpatient services and will personally facilitate the needed assessment and procedures including emergency room evaluations to establish child's safety and possible emergency admissions if that is indicated.

In addition, our team has developed a network of referral sources for youths in need for treatment, including both prevention and treatment agencies within the Mount Sinai Health Care system and in the larger New York City area. Therefore, any individual case of reporting and/or manifesting a need for prevention or treatment services would get individually tailored referral meeting his/her and the family needs.

6.5. Risks associated with MRI scanning: There are few serious risks associated with the MRI procedure. The best protection against these risks is having a well-trained staff who are comfortable working with children and who are familiar with MRI procedures and working in the imaging environment. Participants will be carefully screened to insure that they have no metal implants or other characteristics that would preclude MRI scanning. In addition, prior to the scan, all metal jewelry, body piercings, hairclips, belts, etc. will be removed, as well as, wallets, keys and any other objects that represent a potential risk in the highly magnetized MRI environment. Staff will also be well-versed in ethical standards and will be instructed that if a participant wants to terminate the study, that is what should be done. We use cartoon images as stimuli during the functional scans, and play cartoons or movies for the children during anatomical scans. This tends to increase the level of engagement. The children will enter the scanner in the presence of their parents, and the procedures will be explained to them while they are being prepped for scanning. In addition, participants will be given time to acclimate to the scanner. There is always at least one member of the study staff present with a child during a scan; in cases where scanning is anticipated to be less easily negotiated, 2 staff members may be present. Parents often remain in the scanner area to calm and reassure the children during the scans. However, this is rarely required. Finally, participants will have had an opportunity to acclimate to the fMRI procedures prior to the day of the scan through participation in a "mock

scan" procedure – which simulates the fMRI experience.

The MRI portion of the study presents possible minimal risks. Though for most people the MRI presents very few physical risks, certain factors may increase the risk. MRI scanning has been demonstrated to have potentially negative effects when performed on people who have metal-based tattoos (although this is not a problem with recently obtained tattoos), transdermal patches, or metallic objects or electronics that cannot be removed (for instance, metal fillings, internal electronic devices, etc.). Persons with such risk factors (except non-reactive tattoos) must be appropriately screened and excluded from completing the study because participation might be dangerous for them. For those subjects who do not possess the above contraindications for scanning, the risks posed from MRI scanning are of two types: 1) potential discomfort or distress during scanning, and 2) the possibility of anatomic abnormalities being discovered in the course of scanning (See #5 below). The first risk—fear or discomfort from scanning—is generally greater for young people than for adults. However, we are very experienced in scanning children, and we have developed a very child-friendly facility and scanning protocol. Still, it is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized, first by introducing children to the MRI using a mock scanner, where the rules for the tasks will be explained and the experience of being in a scanner will be simulated (e.g. playing scanner noises) to acclimate the child to the scanner environment. Other strategies include requirement of inserting ear protective devices, using a mirror that enables a view outside the scanner, and using experienced technicians who will monitor all subjects for distress and reassure participants when necessary. In the event that a participant becomes anxious during a scan, the study will be halted. Participants will be able to communicate with the technician at all times using the intercom system should they have concerns or questions during the procedure or to request that a scan be terminated or suspended. The subject will be in full view of the operator at all times. Additionally, participants with fear of enclosed spaces will be excluded from the study.

The risks from the scanner itself can be classified into one of five categories: a) Acoustic Noise Levels, b) Gradient or Time-Varying Magnetic Fields, c) Radiofrequency (RF) Magnetic Fields, d) Static Magnetic Fields, and e) Other.

i) Acoustic Noise Levels: The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process. The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA and ear protective device will be used at all times.

ii) Time-Varying Magnetic Fields: The concern about the time-varying magnetic fields used in MRI is that these can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling.' In very rare instances, this nerve stimulation can be painful. The gradients used in our Skyra 3.0 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances the system will be operated in a way that poses non-significant risk to the participant.

iii) Specific Absorption Rate (SAR): MRI scanning induces some heating of body tissues. This specific absorption rate (SAR) that determines heating is the amount of radiofrequency (RF)

energy deposited (typically by a coil or “helmet”-like apparatus placed over the subject’s head) per Center volume of tissue per Center time. The SAR for RF radiation is primarily related to the amplitude of RF power, the duration of the RF pulse, the type of RF coil used, the frequency of RF radiation, the resistivity of the tissue, the configuration of the anatomical region being examined, and several other parameters. FDA Guidelines: "The following are levels of concern at which the reviewer shall exercise appropriate actions to ensure that the safety of the device is substantially equivalent to a predicate device: A) If SAR = 0.4 W/kg whole body; and if SAR= 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR = 3.2 W/kg averaged over the head: **below level of concern**. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: **below level of concern**. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern." Because all experiments performed on the 3.0 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, this criterion for classification of NSR is satisfied.

iv) Static Magnetic Fields: The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with thousands of clinical studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the subject. Children with these objects will be identified, as described above, and excluded from the scan.

This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI Centers). It is not unique to our 3.0 Tesla facility, which will maintain a safety policy to safeguard subjects and staff members from these incidental risks. Systems with static magnetic field less than 8 Tesla have been considered to represent a non-significant risk by the FDA. The static magnetic field of our system (3.0 Tesla) is therefore to be classified as posing non-significant risk to human subjects.

v) Other Potential Risks: The physical confinement and isolation produced by the scanner could cause emotional distress, although in our past experience, subjects generally tolerate the procedures well.

vi) Incidental findings on MRI: Another possible risk stems from incidental findings that might be detected during scanning. The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. All subjects will be alerted to this possibility during the consent process. Though the type of scan used does not, in general, give adequate information for a clinical quality-read (of which subjects will be informed), if the MRI technologist or experimenter sees something concerning, a radiologist will read the scan for potential gross abnormalities and will report any such findings to the PI, so that the subject may be notified in a timely and appropriate fashion. If an incidental finding arises, parents will be advised to consult with their child’s physician for further evaluation.

If a subject is injured as a result of participation in this research study, emergency care, hospitalization, and outpatient care will be made available by The Mount Sinai Health Care system and billed to the subject/family as medical expenses. No money will be provided by the Institute as compensation for a research-related injury. See also “Protection against Risk” below.

6.6. IRB Approval. Several steps are taken to protect against a breach of confidential information. The collection, use, and sharing of information will adhere to HIPAA regulations, and participants and their parents will be required to sign IRB-approved statements that the HIPAA regulations have been explained to them. This applies to personal health information collected by both the Departments of Radiology and Psychiatry. Participants' names, dates of birth, and other identifying information collected during the proposed study will be stored in source documents. The source documents will be stored in locked file cabinets in the PI's locked office. Information (e.g., rating scales, diagnostic interviews) from the clinical assessments obtained as part of the study will also be stored in the source document folders. Information from the source documents pertinent to the research (e.g., age, diagnosis. etc.) will be entered into and stored in databases. These databases will not contain identifying information and will be indexed by a research code. Data from the fMRI procedures will be downloaded to the study team, or put onto compact discs provided to the PI or his designee. The compact discs will be stored in the locked file cabinet with the source documents. The images from the compact discs will be transferred to a fixed location computer that is password-protected. These computers are connected to the internet through the MSSM network. The images will be indexed by the same research code and contain no identifying information. Computer files containing the data from the fMRI tasks are created with the research code only and contain no identifying information. These computer files will be stored on the same fixed location computer. The research codes will be stored in the participants' source document, thereby providing a link between the research data and the identifying information. Only the PI and the research coordinators working on this project have access to the source documents and the link between the identifying information and research codes.

The study team will obtain Mount Sinai IRB approval and will adhere to all IRB guidelines for protection of human subjects.

6.6.1. External review. Risks to confidentiality also include the possibility of outside review of participant charts by members of the DSMB or by ethical or governments organizations wishing to review charts for data verification purposes. This is explained in the consent form.

6.6.2. Sources of Materials. Behavioral, psychiatric, neuropsychological and neuroimaging data will be collected from children and adolescents. All data collected within the context of this research will be used for research purposes only. Results of the neuroimaging procedure will be used for research purposes only. Structural scans can be made available to qualified professionals, when appropriate, and with the written consent of the participants and their parents.

Study oversight and DSMB. Human subject protection will be ensured by the routine procedures that we have put in place to conduct the study, and also the oversight which is provided by the Data Safety Monitoring Board (DSMB). The DSMB will review all aspects of the study, including recruitment procedures, informed consent, protocol violations, the occurrence and handling of adverse events, and patient outcomes. This information will be provided for review by the senior study coordinator. The DSMB will review this information in blinded fashion; randomization codes will only be examined if there is serious consideration of altering the study design in any way. The DSMB review protects subjects because it oversees the implementation of good clinical and research practices, and monitors the safety of the trial. The DSMB will meet annually and write a report to describe its findings. This report will be shared with the site PIs and filed with the IRB.

6.7.1. Data and Safety Monitoring Plan

a) External DSMB

A DSMB will be put in place to review the conduct and safety considerations of the trial.

b) Composition of the DSMB

The committee for the clinical trial will consist of two clinical researchers who are not directly involved in this project and who have no stake in the outcome of the study. The two members of the DSMB will be psychiatrists who have extensive experience with clinical trials with stimulant and non-stimulant medications for ADHD, and expertise in incorporating fMRI biomarkers into these trials. DSMB members will be compliant with OMB guidelines, will not be employees of Icahn School of Medicine at Mount Sinai, and will have no conflict of interest with this research.

c) Procedures and Responsibilities of the DSMB

Two to four weeks prior to each DSMB meeting, the senior coordinator and data manager will prepare a report to be reviewed during that meeting, under the direction and supervision of the PIs. The report will include the number of participants who signed consent for the study and were randomized, the number of post-randomization dropouts, reasons for these dropouts, and any safety concerns, adverse events, etc. An up-to-date consent form will be provided, as well as a summary of measures taken to protect confidentiality (e.g., data and tape storage, use of coded ID numbers, etc.) The Study Coordinators will also prepare a report summarizing any new data/evidence that might alter the risk/benefit ratio for participating in the study (e.g., newly published studies, etc.) Data will be presented to the DSMB in such a way as to maintain patient confidentiality.

The DSMB will meet via conference call yearly. At an initial meeting, the DSMB will review the research protocol and plans for data and safety monitoring. The DSMB will issue an annual report that summarizes:

(1) All serious and unexpected adverse events (for example, inpatient hospitalizations or ER weeks) or other unanticipated problems that involve risk to study participants or others, and whether these appeared related to the study-based interventions or research assessment protocols. Reports will not specifically disclose the treatment arm of the study unless this disclosure is required for safety reasons. Note that any serious adverse event (SAE) will be reported to the local IRBs and to the DSMB within a 24 hours according to standard regulations.

(2) The committee's judgments as to whether participants' safety, privacy, and confidentiality have been consistently assured by the investigators;

(3) The committee's review of the study's progress toward recruitment goals and participant retention/attrition rates;

(4) Its review of new scientific literature pertinent to the safety of participants or the ethics of research participation (for example, new therapeutic or imaging developments);

(5) Its recommendations as to whether risk/benefit ratios have changed to the extent that the trial should be modified or discontinued. Specific recommendations for protocol modifications will be elaborated, with the accompanying rationale for each.

DSMB reports will be filed with the PIs, who will file them immediately with the IRB. This information is also filed in the annual progress report to NIH. The reports will enumerate the dates that the committee met and explicit procedures for monitoring participants' safety and confidentiality, and data integrity during the

reporting interval.

There will be regular, ongoing communication between the PIs, the IRB, and the DSMB. The PIs will take responsibility for reporting any serious and unexpected adverse events in a timely fashion directly to the DSMB. The PIs will also report serious and unexpected adverse events or other unanticipated study problems to the IRB. Actions taken by IRB in response to adverse event reports will be immediately reported to the DSMB and the NIH Project Officer, if appropriate.

The Mount Sinai IRB (FWA Assurance Number 0005656) will review all required documentation (initial and annual renewal applications, recruitment materials, adverse event reports, etc.) for the Mount Sinai site in this project.

6.8. Safety Monitoring Plan: This protocol presents minor increase over minimal risk to the subjects. The medications to be used in the study are well-established and considered to be safe; serious adverse events are not anticipated. In the unlikely event that such events occur, they will be reported in writing within 24 hours to the local IRB. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an SAE, the participant will be monitored by the investigator via ongoing status assessment until 1) a resolution is reached, i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected, 2) the SAE is determined to be clearly unrelated to the study intervention, or 3) the SAE results in death. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIH.

The PIs will be responsible for evaluating the adverse events and study data at regular intervals and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent form are required. During the review process, the PIs will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the PIs or the IRB have the authority to stop or suspend the study or require modifications. The review of all adverse events by the PIs will determine the attribution and grade of severity of the adverse event by using the following scales:

Attribution of Risk Categories.

Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention

Probable: Adverse event(s) will likely be related to investigational agent(s)

Possible: Adverse event(s) may be related to investigational agent(s)

Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)

Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Grades of Risk.

0: No adverse event or within normal limits

1: Mild adverse event

2: Moderate adverse event

3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect

4: Life-threatening or disabling adverse event

5: Fatal adverse event

6. Clinicaltrials.gov Requirements

The proposed study does not meet the requirements as an applicable clinical trial.

Clinicaltrials.gov Requirements.

The proposed study meets the requirements for an applicable clinical trial. Once approved, the study will be posted in clinicaltrials.gov. Updates will be provided as appropriate.

Overall Structure of the Study Team

Qualifications. The team has an extensive record of research on the neurobiology and pharmacotherapy of ADHD, as well as expertise in the use of fMRI to examine activation in the reward system in youth with ADHD and varying SUD risk. Drs. Newcorn and Ivanov have an established record of recruiting youth with ADHD who are scanned pre- and post-treatment, and has published one of the very few treatment studies in ADHD directly comparing MPH and ATX using fMRI. We have also successfully recruited drug-naïve youth with ADHD at HR and LR for SUD. Drs. Shulz and Fan have been close collaborators with the PIs on this project as evident from our publication record. They will provide expertise on quality control and analyzing of the neuroimaging data.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

Children with attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD) are known to have elevated risk for adolescent-onset substance use disorders (SUD), and those with comorbid ADHD + ODD/CD are at greatest risk. Stimulant medications such as extended release mixed amphetamine salts (MAS-XR) and non-stimulant medications (e.g. atomoxetine or guanfacine) have established efficacy for ADHD and are also beneficial for ODD/CD. However, stimulants have direct effects on the brain reward system, and abnormal reward processing is thought to mediate addiction vulnerability. Although longitudinal studies have not shown increased SUD risk in youth with ADHD treated with stimulants, it remains unknown whether stimulants might have differential effects on reward processing in high risk (HR) vs. low risk (LR) populations.

fMRI offers a cost effective method of evaluating covert effects of stimulant medications for youth with ADHD and SUD risk by examining pre- to post-treatment changes in activation in the brain reward system that predate exposure to drugs of abuse. This approach is supported by the results of studies, which indicate altered (mostly elevated) sensitivity in the reward system in youth at-risk for SUD; high activation in the reward system has in turn been linked to problem drug use. However, to date, no study has examined changes in the reward system with stimulant treatment in youth with ADHD and high vs. low risk for SUD, who have never been exposed to stimulant treatment or drugs of abuse. Such research could provide important knowledge regarding the biological basis of addiction vulnerability and guide treatment selection.

Our team is in an excellent position to study differences in activation in the brain reward system during fMRI before and after treatment with MAS-XR in young children (7-12 years old) with ADHD, who are naïve to both stimulant treatment and drugs of abuse, divided into LR (i.e., ADHD only) and HR (i.e., ADHD + ODD/CD) groups. We will confirm that youth with ADHD/HR status have exaggerated activation in the reward network compared to ADHD/LR youth and controls, and test competing hypotheses regarding the effects of the two medications on the brain reward system, and across the different risk groups. This protocol is innovative in its approach to study young, drug-naïve children at various levels of SUD risk, and is highly significant in its use of neuroimaging to delineate possible differential effects of stimulant and non-stimulant medications on reward processing in youth with ADHD and HR vs. LR for SUD as a biomarker of treatment-related risk. This research will substantially advance our understanding of the biological basis of vulnerability for addiction, and aid in the development of treatment recommendations for youth with ADHD and varying levels of SUD risk.

4.2. Study Design

4.2.a. Narrative Study Description

Childhood ADHD and comorbid oppositional defiant disorder (ODD) and conduct disorder (CD) are considered risk factors for subsequent substance abuse, and youth with both ADHD and ODD/CD are at greatest risk. However, the effects of treatment of ADHD with stimulant medications such as methylphenidate (MPH) and mixed amphetamine salts (MAS) on risk for substance abuse are poorly understood. We propose to use fMRI to study the effects of extended release mixed amphetamine salts (MAS-XR) in drug-naïve youth 7-12 years at low risk (i.e., ADHD only) and high risk (i.e., ADHD + ODD/CD) for substance abuse on the brain reward system, to better understand the potential impact of these medications on an aspect of brain functioning which is thought to underlie vulnerability to substance abuse.

4.2.b. Primary Purpose: Prevention

4.2.c. Interventions

Type	Name	Description
Drug (including placebo)	Mixed Amphetamine Salts	This is an FDA approved treatment for ADHD

4.2.d. Study Phase: Phase 4

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model: Single Group

4.2.f. Masking ○ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation N/A

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	fMRI activation during a behavioral 'ACR' task	Pre and Post 3 weeks	C.7.2. Task paradigms. The ACR is an event-related task that provides 3 temporally distinct probes of reward anticipation, conflict resolution, and reward outcome. It consists of four 32-trial blocks, each 6 minutes long. There are 2 cue types (reward/non-reward) followed by congruent/ incongruent flankers: both cue and flanker trials are counterbalanced and are fully orthogonal. Participants are required to respond as quickly as they can to the direction of the central arrowhead while ignoring the flankers. Correct responses in trials beginning with reward cues yield $1 reward. Incorrect or slow responses are followed by a $1 loss. The ACR task provides only 25% money wins and introduces reward violation (unexpected non reward) in 25% of the trials, which results in strongly engagement of the insula, ACC and also putamen predominantly during reward outcomes.

4.4. Statistical Design and Power Design and power-NEW-6.22.18.pdf

4.5. Subject Participation Duration 3 weeks

4.6. Will the study use an FDA-regulated intervention? ● Yes ○ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status Availability of product.pdf

4.7. Dissemination Plan Dissemination plan.pdf

Brief summary

We propose to study the effects of 3 weeks of treatment with MAS-XR on the brain reward system in youth with ADHD only (LR) vs. ADHD + CD or severe ODD (HR). We will study 36 treatment- and drug-naïve youth (18 per risk group) ages 7 – 12 years. LR and HR subjects will be assessed with clinical and neuropsychological measures and will be subjected to fMRI scans twice – before and after 3 weeks of treatment with mixed amphetamine salts- extended release (MAS-XR). The fMRI scans will be conducted while participants perform the Anticipation, Reward, Conflict (ACR) task developed by our group, which has a unique component of unexpected non-reward. Combining prediction error analyses with purported activation differences on this particular component of the ACR will offer a never before explored approach to assess differences between youth at different risk levels for SUD. Importantly, our event-related design will distinguish increased effort and associated anticipatory activation (a positive effect) from increased hedonics of reward (a potentially deleterious effect).

Study design

This is an open label trial which will recruit two groups of drug naïve youth ages 7-12. The Low Risk (LR) group will consist of children diagnosed with ADHD only and the High Risk (HR) group will consist of children diagnosed with ADHD and severe ODD or CD. Both groups will receive treatment with Mixed Amphetamine slats (MAS-XR) and will undergo two fMRI scans – the first scan will be performed before treatment and the second will be performed after 3 weeks of treatment. The main outcome measures will be the activation in brain regions indexed by the fMRI while the participants perform a reward task in the scanner

Study Periods The study will consist of 5 visits including screen, baseline and 3 treatment visits. Participants will be scanned at visit 2 and rescanned at visit 5. They will receive treatment with MAS-XR with flexible dosing. The main goal of the treatment is to index purported changes in the activation of the brain reward circuits as changes in BOLD signal will be our primary outcome. We will also assess for changes in ADHD symptoms and medication adjustments will be guided by changes in those symptoms. Therefore the objective of the study is to index changes in BOLD signal pre to post treatment with MAS-XR which is a first line medication for the treatment of ADHD and has known abuse potential

Study Period I: Screening/baseline (Visits 1–2). The 1st and 2nd visits both involve assessment; the 2nd visit also includes the baseline fMRI scan. Subjects will have a “mock scan” at the 1st visit, following established guidelines. We anticipate that the assessment procedures can be completed in 2 study visits within 14 days. The screening period can be lengthened to accommodate washout of a non-stimulant drug if this is required.

Study Period II: 2 Week Treatment Block (Days 0 to 21)**.** Subjects will receive open label treatment with MAS-XR for 3 weeks. Medication will be titrated using a fixed dose approach, with doses that mimic those used in clinical practice. The two assigned doses are 0.25 mg/kg and 0.5 mg/kg, with an option to increase to 1.0 mg/kg if needed. At study completion, participants will complete the post-treatment fMRI scan and all clinical measures. There will be 2 visits during this period - one after 1 week of treatment and one at 3 weeks (EOT). There will be a phone visit at the end of the second treatment week, though subjects can be seen if necessary.

Study medication and medication administration. Subject treated with non-stimulants will be required to be off medication for 2 weeks prior to scan. We will purchase MAS–XR, an extended release generic amphetamine formulation. Subjects will begin at 0.25 mg/kg and increase to 0.5

mg/kg after one week. This dose can be reached (within ~5 mg) using 2 capsules of commercially available doses. Those who cannot increase the dose due to AEs will be allowed to maintain their dose and be evaluated for a dose increase after 2 weeks. Subjects who experience difficulty with symptom control can titrate to a higher dose if need be (maximum 1 mg/kg). Subjects who increase their dose and experience AEs will be allowed to lower their dose. Subjects will receive MAS–XR on the day of the second scan approximately 6-8hrs before scan.

Data Analysis

First level (within-subject) analyses will be conducted for each participant with a general linear model (GLM) to quantify the relationship between the observed event-related BOLD signals and regressors encoding expected trial-specific responses. The design matrix will be comprised of 12 regressors: 2 for cue (reward vs. non-reward) x 2 for target type (congruent or incongruent flankers) x 3 for outcome-related effects (reward, non-reward, punishment). There are 4 outcome contrasts of interest: reward following reward cue, non-reward following reward cue, non-reward following non-reward cue, or punishment for an incorrect/missing response.

Group-level Statistical Analysis. Descriptive statistics (e.g., means, standard deviations (SD), etc.) for all variables of interest will be computed and compared by Student t test for continuous variables or Chi-square test for categorical variables. Group statistical analyses of the imaging data will be performed using a GLM from SPM. The GLM is written as Y=XB+E, where Y is a matrix with a series of multivariate measurements, X is a design matrix, B is a matrix containing parameters that are usually to be estimated and E is a matrix containing errors or noise. The errors are usually assumed to follow a multivariate normal distribution

Primary Aim. We will test two hypotheses: 1a) the HR group will show greater baseline activation than LR (during the ACR task) in the insula, putamen, and ACC); 1b) MAS-XR treatment will reduce the activation in the brain reward system for both groups, possibly in greater magnitude for HR. We will run F-tests of the voxel-based whole brain activation pattern with ANCOVA controlling for time (baseline, post-treatment) with two groups (HR, LR) with age, sex, IQ and medication dose level included as covariates. We will run independent t-test to compare activation at baseline and at and of treatment between HR vs. LR participants. The voxel-based Z statistic images will be thresholded using clusters determined by $Z>2.3$ and a cluster corrected significance threshold of $p<0.05$.

Exploratory Aim. We will conduct correlation analyses between pre to post- treatment measures of activation in the reward system and scores on the behavioral measures collected outside the scanner (i.e., Kirby, BIS/BAS, UPPS) to examine the direction and magnitude of correlations between brain function and behavior.

Power analyses. The main power considerations for the primary aim are related to the ability to detect differences in activation between the two groups pre- to post treatment. We estimated power using Monte Carlo simulations (10,000 draws per model), with $\alpha = 0.05$, for all models. With a between subjects factor (2-levels; LR, HR) and *4* covariates (age, sex, IQ, *dose level*), we were able to recover large effects sizes (f = .80-1.0) for the between group factor with 40 ADHD subjects, which corresponds to approximately a .8-1 difference in activation. For the exploratory aim, we used regression models with the behavioral measures, the same 4 covariates, using the baseline level of each behavioral measure to control for time effects and activation as the dependent variable. In the simulations, we were able to recover effect sizes of *d* =.2-3 with 4-5 independent nuisance covariates (age, sex, IQ, does), and baseline covariates with a correlation of .35 in the model.

MAS –XR is FDA approved and is available through the investigational drug service.

Dissemination plan

The Co-Principal Investigators are committed to the development of large, shared data bases which can be used to study the neurobiological basis of substance abuse risk. This is very much in line with the current efforts of NIDA to launch the Adolescent Brain Cognitive Development (ABCD) Study, which we feel the proposed research will complement and augment. We appreciate that the public dissemination of our scientific results will potentially facilitate the creation of collaborative efforts, with outside investigators playing an important role in helping to further understand the topics to be addressed in this research. Research data will be shared according to the most recent NIH guidelines (http://www.ott.nih.gov/policy/rt_guide_final.html).

We are mindful that the rights and privacy of people who participate in research must be protected at all times, that there is the need to protect patentable and other proprietary data, and that restrictions on data sharing may be imposed by agreements with third parties. In this regard, Icahn School of Medicine at Mount Sinai is and will remain HIPAA compliant, and therefore any datasets resulting from human participant research will be free of any identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of individual subjects.

Timelines for distribution of data will vary depending on the nature of the data to be shared and any required restrictions. In addition to communication channels such as speaking engagements and publications, data may be distributed by a number of electronic methods, including web-based databases, datasets, and spreadsheets, or via electronic media such as CDs, DVDs, and tape. The method(s) of distribution employed will be determined at a later date.

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

Roles/Areas of responsibility of the Principal Investigators (PIs)
As joint PIs, Drs. Jeffrey Newcorn and Iliyan Ivanov will be jointly responsible for the scientific direction and productivity of the research study. The multiple PI structure reflects the unique expertise each brings to this project, their successful history of joint leadership, and the joint collaboration on this project. Dr. Newcorn is a board certified child and adolescent psychiatrist and developmental cognitive neuroscientist with vast experience in childhood psychopathology and pharmacological treatment of neurodevelopmental disorders in childhood and adolescence. He has an extensive history of NIH funding and scientific research in the area of neuroimaging (functional and structural MRI and DTI) as well as longitudinal studies of children with ADHD; he is currently PI of a R01 grant investigating brain activation and connectivity differences associated with stimulant and non-stimulant pharmacological treatments for ADHD. He is experienced with administrative duties related to large-scale clinical research projects. Dr. Ivanov is a board certified child and adolescent psychiatrist and developmental cognitive neuroscientist who has completed a NIDA K-12 Award for which Dr. Newcorn was the primary mentors. He has extensive clinical experience in the assessment and treatment of adolescent SUD and is an expert in implementing neuroimaging techniques for the study of biological markers of clinical risks for later SUD. Both PIs will have joint decision-making authority with respect to administration. The scientific aims of this project are best served by the combination of these areas of expertise.

Fiscal and management coordination:
The PIs will jointly provide oversight of the entire proposed project and development and implementation of all policies, procedures, and processes. As such, both PIs will be responsible for the implementation of the research plan, achievement of the specific aims, and institutional compliance regarding human subjects. They will be jointly responsible for fiscal and research administration, including human subjects approval, participant characterization and will jointly oversee MRI data collection and analysis. Given his significant administrative experience, Dr. Newcorn will serve as contact PI and be responsible for all communication with NIH, including submission of progress reports.

Process for making decisions on scientific direction and allocation of resources:
The PIs will hold weekly meetings to discuss experimental design, data analysis, and all administrative responsibilities. They have published several papers together. They keep in daily contact via email and phone. Given their long standing collaboration history they will work closely together with equal decision-making power to consider and discuss any changes in the direction of the research projects, including the reallocation of funds, if necessary.

Data sharing and communication among investigators:
Both PIs will share their respective raw, de-identified data and research results with each other and key personnel. This data sharing will be facilitated through the existing data coordination/sharing processes in place for all current collaborations between the PIs.

Publication and intellectual property (if needed) policies:
Publication authorship will be based upon the relative scientific contributions of the PIs and key personnel, consistent with current Sinai and NIH policies.

Procedures for resolving conflicts:
If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement will be referred to a multiple PI arbitration committee composed of faculty of ISMMS. Any Chairs, Institute Directors or Division Chiefs on the committee must recuse themselves if any of the PIs have appointments in their department,

institute, or division, respectively. The committee will be co- chaired by the Dean for Research Operations and Infrastructure and the Dean for Translational Biomedical Research. All PIs agree that any decisions made will be final and binding.

Change in PI Location.

If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that a PI cannot carry out his or her duties, a new PI will be recruited as a replacement at one of the participating institutions by the remaining PI and the PI that is relocating.

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