Imaging Stimulant and Non-Stimulant Treatments for ADHD: A Network-Based Approach
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Brief Summary of Research (250-400 words):

The growing number of medications used to treat attention-deficit/hyperactivity disorder (ADHD) raises important questions about whether different medications have similar or different therapeutic mechanisms of action. We have recently shown that the stimulant methylphenidate (MPH) and the non-stimulant atomoxetine (ATX) produce clinical improvement via a common mechanism in motor cortex, and distinct actions in frontostriatal and midline cingulate-precuneus regions. These exciting findings offer a window into the common and unique neurophysiological mechanisms of response to stimulant and non-stimulant treatments. However, the interpretation and clinical utility of these results would be greatly enhanced by in-depth investigation of the impact of the two treatments on relevant neural networks, and analyses which evaluate whether improvement is achieved via normalization or other adaptive changes in brain function. In addition, it would be useful to examine the relationship between a variety of demographic and clinical characteristics (e.g., age, sex, adhd symptom severity, etc) and fMRI profiles pre-treatment. Assessing this question requires a relatively larger data set. Which can best be achieved by combining the data from the various studies indicated.

1) Objectives:

Research Question:

The **specific aims** of this project are to use functional magnetic resonance imaging (fMRI) to determine the significance of activation changes over treatment related to clinical improvement, and the impact of treatment on neural connectivity within and between the anti-correlated frontostriatal 'task-positive' circuit and cingulate-precuneus 'task-negative' network. Our central **hypotheses** are that clinical improvement is associated with: (i) normalization of reduced connectivity of regions within the 'task-positive' network, with resultant increased inhibition of motor cortex, and (ii) normalization of low task-related connectivity in regions within the task-negative network for MPH and the 'task-positive' network for ATX.

This research proposes to test a model which posits a neurophysiological basis of mechanisms of response to stimulant and non-stimulant medications, and fits with our **long term objectives** of being able to match treatments to individual patients. Testing this model requires large samples of youth scanned using fMRI before and after treatment, and matched healthy controls also scanned twice. We will use an innovative network-based approach to study the effects of treatment, building on results from our current fMRI treatment study, and incorporating new theoretical approaches to understanding ADHD and its treatment.

In addition we now wish to examine the relationship between a variety of demographic and clinical characteristics (e.g., age, sex, adhd symptom severity, etc) and fMRI profiles pre-treatment.

2) Background

The increasing number of medications used to treat ADHD in children raises important questions about the mechanisms by which these different classes of compounds exert their therapeutic effects. This project will establish the therapeutic mechanisms of action of the stimulant methylphenidate and non-stimulant atomoxetine, by answering two key questions: 1) to what extent do effective treatments result in "normalization" of aberrant brain pathophysiology and/or new "adaptive" or compensatory changes in neurophysiology - focusing on the interactions between neural networks implicated in ADHD; and 2) what are the common and unique mechanisms of action of the two medications on 'task-positive' and 'task-negative' neural networks?

In addition, there are few studies which have used fMRI to examine the relationship between a variety of demographic and clinical characteristics (e.g., age, sex, adhd symptom severity, etc) and fMRI profiles pre-treatment.

3) Setting of the Human Research

Participants will be consented and evaluated at Mount Sinai in the department of Child and Adolescent Psychiatry in the 19 East 98th Street building, 5th floor-Room 5E. The fMRI scans will be conducted in the Radiology department, Translational and Molecular Imaging Institute (TMII).

Participants are only recruited through the existing protocols and no additional participants will be recruited and consented for the combined data set without prior approval from the PPHS.

4) Resources Available to Conduct the Human Research

Beth Krone, PhD and Jeffrey Newcorn, MD, will follow all subjects in the study, along with supervised medical trainees from the Icahn School of Medicine, who are to be determined. Study coordinators and research assistants will assist in following subjects and fMRI scanning. Staff from clinics and practices within the Mount Sinai Health System will assist with patient referrals. Kurt Schulz, PhD will supervise all fMRI scanning and scan data collection.

Beth Krone has worked in Dr. Newcorn's lab since 2008. Dr. Krone is a clinical psychologist with extensive prior experience in clinical research, cognitive and neuopsychological assessments, and group and individual counseling. She

completed her certificates for Human Research Protection, HIPPA, and Research Data Security, as well as "Basic IRB Training for Clinical Research Coordinators" and CITI-training modules for Mount Sinai.

In addition to personnel and facilities that are being used to continue the activities performed under the NIH grant R01MH095766, the research team has access to existing, de-identified datasets that contain baseline clinical, behavioral, and fMRI data from children and adolescents ages 7 to 17 years old who participated in Investigator Initiated trials (GCOs 02-0243, 03-1169, 04-0059, and 09-1825). The investigators will use this baseline data to augment the sample size, and increase power of the analyses.

Note that no clinical assessments will be conducted outside of these protocols for inclusion as part of the combined data set that will be used for additional analyses that were approved on 9/19/16 by the PPHS. We will simply be examining aggregate de-identified data across studies for these additional analyses.

5) Study Design

a) Recruitment Methods

Youth will be recruited for the treatment study using multiple methods to ensure representativeness:

- ResearchMatch will be used as a method for identifying and contacting potential subjects. The study specific announcement is included with this submission.
- We will publicize the study to colleagues at our institution throughout the Mount Sinai Health system, including our research partners and clinical programs
- We will contact past participants of GCO 03-0612, 09-1825, and 10-0435 studies who indicated on their consent forms that they would like to be contacted regarding future studies.
- Dr. Halperin, Co-I on this study, has been conducting an NIH-funded longitudinal study of preschool children who were deemed to be either at risk for ADHD or typically developing when they were 3-4 years-old (R01 MH068286-08) for the past 8 years at Queens College/CUNY. Currently, the majority of these children are between the ages of 8 and 11 years-old, and approximately 75 of them met diagnostic criteria for ADHD at their last evaluation. Although diagnosed with ADHD, these children do not receive treatment from his study, although it would likely be advantageous for many of them. As such, this sample may serve as a source of referrals for this study at Mount Sinai. The IRB at Queens College allows Dr. Halperin to post fliers for other related research studies on the bulletin board in his waiting

room, and in the past, his study parents have participated in several of these posted studies.

- We will advertise in the electronic (e.g., Craig's List) and news media, and post the study on relevant web sites (e.g., Center Watch; CHADD, AACAP, etc.).
- We will make information about the study known to the potential target audience by mailings from the local chapter of CHADD, mailings to clinic directors, as well as mailings to local pediatric and psychiatric practitioners.
- We will include information about study recruitment in lectures given in academic and community settings, and through a series of educational and outreach efforts to be conducted in our local communities.
- Study coordinators will also contact school psychologists at *private and parochial* schools for potential referrals.
- Word of mouth

All advertisements and letters used for recruitment will be submitted to the IRB for approval and a script for recruitment in the Outpatient Clinic has been included with the application packet. The script provided to the clinic contains other referral options both within and outside Mount Sinai. The study is not represented as the patient's only potential option for care.

School psychologists will be provided with material from the Mount Sinai ADHD Center, the outpatient clinic, and IRB approved materials that discuss the research program. The school psychologist may choose to distribute the information to parents and guardians. We offer materials for counselors to offer parents during their routine feedback sessions, AND WILL MAKE IT CLEAR THAT RESEARCH IS AN OPTION. This does not introduce any additional risk to the common practice of teachers' routine identification of children in need of intervention in their classrooms. Each school will have its own procedures for how the teachers and counselors proceed with offering recommendations and resources to parents of these children. The site will respond to telephone and email inquiries from any school personnel; however, the site will never contact potential participants based on these referrals without their prior knowledge. Either the referral clinician will ask the participant to call the site or the referral source will seek approval from the parent prior to a request for the site to call.

When initial contact is made, the participant's eligibility will be assessed using a questionnaire/screener. Our current pre-screening form was designed in collaboration with, and approved by, our PPHS to meet their criteria precluding requirement of consent. With it, we inform the parent about specific inclusion/exclusion criteria and the symptoms of ADHD, ask the parent's opinion about whether the child meets these criteria, and obtain the identifying information necessary for scheduling appointments that are required for screening (CRC nursing and mock scanning). To meet PPHS criteria to preclude consent, we: 1) record all identifying information on a page separate from the remainder of the document, so

that it can be dissociated from any response notes about the inclusion/exclusion criteria. Thus, any notes about whether the parent feels the child can swallow pills, will agree to urine testing, or has symptoms of ADHD, etc., are not identifiable; and 2) We place a notice on the forms to instruct staff to refrain from using for research any of the de-identified notes, or the identifying information necessary for administrative purposes. This reads as: 'This form is not to be used as research data!' The pre-screening form is essential for educating potential participants about the study inclusion and exclusion criteria, reducing the number of children who go through a rigorous screening process when they are clearly not going to meet inclusion/exclusion criteria, and collecting the administrative information required by CRC and the TMII. It is not a research tool, and it is not used as information during the actual screening. Identifying information regarding the participant will not be recorded on the screen if potential eligibility is unlikely and/or the participant has no further interest in the study or future studies. We will unlink the pre-screening information from the identifying information. Only an IRB-approved screen will be used. A copy has been provided with the submission packet.

No new recruitment will be done for the assessments done in the combined data set.

b) Inclusion and Exclusion Criteria

General inclusion criteria for subjects with ADHD and healthy controls are:

- aged 7-17 years;
- Wechsler Intelligence Scale for Children (WISC) scores ≥ 75;
- informed consent and assent to study participation.

General exclusion criteria are:

- history of head injury with loss of consciousness or any CNS disease that is likely to affect brain function;
- diagnosis of autism or pervasive developmental, psychotic, major mood, and Tourette's disorder;
- alcohol or drug abuse in the past 3 months or a positive urinary toxic screen on initial evaluation;
- use of psychotropic medication within 2 weeks of the study (8 weeks for fluoxetine);
- pre-existing medical or psychological condition which precludes being in the scanner (e.g., claustrophobia, morbid obesity);
- metal in the body that cannot be removed (e.g., braces, metal plate);
- positive urine pregnancy test.

Specific inclusion criteria for youth with ADHD are:

- diagnosis of ADHD, any subtype, determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL);
- ADHD Rating Scale-IV-Parent Version: Investigator Administered (ADHD-RSIV) total score ≥ 1.5 SD above age and gender means for subtype
- Clinical Global Impressions–ADHD–Severity (CGI-S) score ≥ 4;
- ADHD must be the primary diagnosis and focus of treatment, and the treatments offered in the study must not be contraindicated for the comorbid disorder.

Specific exclusion criteria for the treatment trial include:

- previous unsuccessful trial of MPH or ATX that was adequately dosed (≥ 1 mg/kg for MPH or 1.0 mg/kg for ATX) and of adequate duration (≥ 4 weeks);
- abnormal findings on physical exam, or vital signs
- pulse and blood pressure > 95% of age and gender mean;
- inability to swallow capsules;
- weight is < 20 kg or > 85 kg.

Specific inclusion/exclusion criteria for control youth include:

- no past history or current diagnosis of any psychiatric disorder, determined by the K-SADS-PL interview ADHD-RS-IV and CBCL scores for each symptom domain ≤ 1 SD of age and gender means.

c) Number of Subjects

In the current study, eighty subjects with ADHD will be enrolled for assessment; of these we expect 60 to qualify for the pre-treatment fMRI scan. Only those who are successfully scanned (approximately 52) will be randomized to treatment. It is expected that 40 of these will complete the full clinical trial and the post-treatment fMRI scan.

Sixty four sex, age- and gender-matched healthy control subjects will also be enrolled for assessment. It is expected that 56 will qualify as healthy controls, 48 will be able to complete the baseline fMRI scan, and 40 will return for repeat scanning and complete the time 2 scan

In addition to these participants, the combined data set will include deidentified data from the above named studies.

d) Study Timelines

First Patient, First Visit: September, 2012

Last Patient, First Visit: September, 2017

Last Patient, Last Visit: November, 2017

Completed Manuscript: July, 2019

e) Study Endpoints

Baseline and End-of-Study assessment measures:

- Clinical Global Impressions-Severity (CGI-S)
- Child Behavior Checklist (CBCL)
- Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV)
- Attention Networks Test (ANT)
- Continuous Performance Test (CPT)
- Finger Windows
- Digit Span
- Columbia Suicide Severity Rating Scale (CSSRS)
- Atomoxetine-Stimulant Side Effects Rating Scale (ASSERS)
- fMRI procedures with go-nogo task, diffusion tensor imaging (DTI) and resting state
- Conners' Parent Rating Scales Revised- Short Version (CPRS R:S) and Conner's Teacher Rating Scales Revised – Short Version (CTRS R:S) questionnaires (baseline only)
- Weiss Functional Impairment Rating Scale Parent-Report (*WFIRS*-P) questionnaire
- ECG as considered necessary at screening by Dr. Newcorn

f) Procedures Involved in the Human Research

Procedures for research include routine medication visits (reporting of related and non-related symptoms, evaluation of medication tolerance, dispensing of study medication and collection of empty study medication packages for drug accountability procedures) participant interviews, questionnaires and fMRI scans.

- Informed Consent/HIPPA NOPP
- Hollingshead Index for socioeconomic status
- Collection of Patient Demographics
- Mock Scan
- Kiddie SADS-Present and Lifetime Versions (K-SADS-PL)
- Clinical Global Impressions - Severity (CGI-S)
- Clinical Global Impressions - Improvement (CGI-I)
- Child Behavior Checklist (CBCL)
- Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV)
- Wechsler Individual Achievement Test–Second Edition (WIAT-II)
- ADHD Rating Scale-IV-Parent-Investigator Version (ADHD-RS-IV)

- Atomoxetine – Stimulant Side Effect Rating Scale (ASSERS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Social Skills Rating System (SSRS) questionnaire – parent version
- Weiss Functional Impairment Rating Scale Parent-Report (*WFIRS*-P) questionnaire
- Conners' Parent Rating Scales Revised- Short Version (CPRS R:S) and Conner's Teacher Rating Scales Revised – Short Version (CTRS R:S) questionnaires
- Handedness Questionnaire (adapted from the Edinburgh inventory, Oldfield 1971)
- Blood for Genetics analyses
- Finger Windows Test
- Attention Network Test (ANT)
- Continuous Performance Test (CPT)
- Digit Span Test
- Vital Signs: Height, Weight, Pulse, BP, Temp
- Urine Pregnancy Test (post menarchcal females only)
- Urine Toxicology
- Physical Exam
- Concomitant medications
- fMRI procedures with Go/No-Go task, diffusion tensor imaging (DTI) and resting state
- ECG or additional examinations as indicated for clinical clearance in cases with past or family history

Results of pregnancy and drug screening will be shared with parents only when there is compelling reason to do so.

g) Specimen Banking

Upon enrollment each participant will receive a participation identification code. This code will be utilized to label all blood samples collected by the MSSM CRU. The research staff and the CRU staff will have access to the personal identification code. A participant contact log will be established in the form of an electronic record. This log will link the participant's name, date of birth, guardian, and contact information with the participant identification code. This document will be password protected on a shared hard drive. Only the participant identification code will be utilized to establish participant records in the database. Access to these contact logs will be reserved for the coordinators assigned to this project and the P.I.

The blood samples will be collected and stored at 4 degrees in a refrigerator and banked in locked cabinets until processed for DNA extraction. After the extraction all DNA samples will be stored in locked – 80 degree freezer. Numbered DNA

specimens will be shipped via UPS, packaged in dry-ice, to the attention of Ed Cook at the University of Chicago, Illinois for further analysis. Once there, the samples are given an internal lab identification number. The data that are generated will be sent to Mount Sinai under the Cook lab's ID number, which will then be reverted to the original participant ID number. Thus the data will not be identifiable.

Patient preferences indicated on the consent form will guide whether samples will be stored for future use, whether other researchers at Mount Sinai or from other institutions may request access to the samples, and whether the samples may be analyzed for the purposes related to, or unrelated to the study. Requests from other researchers for analysis of the specimens will be considered by the PI, and must receive IRB approval before consideration.

To ensure that adequate provisions are in place for obtaining consent from participants, we will re-consent subjects that turn 18 while enrolled in the study. After a failed good faith effort to contact the child, samples will be de-linked.

To ensure that adequate provisions are in place to safeguard the confidentiality of data and the privacy of subjects, specimens and/or data that is collected will not be used for dbGAP studies.

h) Data Management and Confidentiality

Participants' names, dates of birth, and other identifying information will be collected and stored with the source documents. The source documents will be stored and locked in filing cabinets in the locked research coordinator offices at 19 East 98th Street. Information (e.g., rating scales, diagnostic interviews) from the clinical assessments performed as part of the study will also be stored in the source documents.

A participant contact log will be established in the form of an electronic record. This log will link the participant's name, date of birth, guardian, and contact information with the participant identification code. Access to these contact logs will be reserved for the coordinator assigned to this project and the P.I.s.

Information from the source documents pertinent to the research (e.g., age, diagnosis, results of rating scales and fMRI scans) will be entered into and stored in electronic databases (fMRI data is stored separately from clinical data). These databases will not contain identifying information (no names, social security numbers, or addresses) and will be indexed by a research code.

Study office computers are connected to the internet through the MSSM network server and the PIs, Co-Is, and research coordinators, as well as data manager at MSSM have access via a password. By "MSSM Network Server" the investigator means a folder on the network server that has appropriate levels of protection, is behind the firewall and is backed up and maintained by the IT department, and is accessible only to authorized members of the research team. Backup files and files

to be otherwise disseminated use appropriate encryption per these guidelines established by Sinai IT: " If use of a cloud service is absolutely required, the data must be encrypted before it is sent up the cloud service (encrypted PDF, Truecrypt/McAfee encrypted files)."

Mount Sinai standards require that we retain data for a minimum of 6 years after the date of publication of a manuscript. Data may be kept longer in the event of protocol modifications.

In constructing the combined data set, participant confidentiality will be protected by the use of de-identified data.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

A DSMB will be put in place to review the conduct and safety considerations of the trial. The committee for the clinical trial will consist of clinical researchers who are not directly involved in this project and who have no stake in the outcome of the study. Two members of the DSMB will be psychiatrists who have extensive experience with ADHD clinical trials: Dr. Floyd Sallee and Dr. Chris Kratochvil.

Dr. Sallee is an experienced pediatric psychopharmacologist with board certification in Child Psychiatry and Clinical Pharmacology. He received his M.D. from Southern Illinois University and his Ph.D. in Pharmacology from University of Pittsburgh. He has received funding as Principal Investigator from both the NIMH and NICHD for research in Attention Deficit Hyperactivity Disorder, including the study of anti psychotic pharmacotherapy for ADHD. Dr. Sallee has been mentor and co-mentor on several NIH-funded career development awards. He is currently Professor of Psychiatry at University of Cincinnati.

Dr. Kratochvil is an experienced Child and Adolescent Psychiatrist. He is currently Director of the Division of Child and Adolescent Psychiatry and Professor of Psychiatry and Pediatrics at the University of Nebraska Medical Center. He is on the National Board of Directors for the American Academy of Child & Adolescent Psychiatry, Vice President of the IRB at Children's Hospital/University of Nebraska Medical Center, editor of the Brown University Child & Adolescent Psychopharmacology Update, and sits on the American Psychiatric Association's Council on Children, Adolescents, and Their Families.

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

- 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.

- The committee's judgments as to whether participants' safety, privacy, and confidentiality have been consistently assured by the investigators
- The committee's review of the study's progress toward recruitment goals and participant retention/attrition rates
- 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)
- 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.

These DSMB reports will be filed with the PIs, who will file them immediately with the IRB. The annual reports will also be filed with the NIH Project Officer and the NIH Office for Human Research Protections (OHRP). The reports will enumerate the dates that the committee met and its explicit procedures for monitoring participants' safety and confidentiality, and data integrity during the reporting interval.

There will be regular, ongoing communication between the PIs, 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 NIMH Project Officer and OHRP office.

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.

j) Withdrawal of Subjects

Subjects are permitted to stop their child's participation in this research study at any time without any penalty or without negative affect to their child's ability to receive medical care at Mount Sinai or to receive any benefits to which they are otherwise entitled. The PIs may also withdraw a participant from the study.

PI may withdraw participants from the study due to non-compliance, poor tolerability/adverse event, or other circumstances in which the PI believes continued participation would be unethical or detrimental to the child, the family, or to the integrity of the study.

For the combined data set, participants have already consented to having us use their de-identified data.

6) Risks to Subjects

There is some physical risk to participation in the study, since children and adolescents will receive treatment with MPH or ATX. Although the experience of at least some side effects may occur, side effects are usually mild and subside after initiation.

Common side effects of stimulant medications include: insomnia, loss of appetite, irritability, headache, occasional dysphoria, and tics.

Common side effects of ATX include sedation, abdominal pain, loss of appetite, and nausea.

Other more serious adverse effects can sometimes be seen.

In addition, there are also risks and discomfort associated with venipunctures.

Additional risks are related to confidentiality of personal information. Every effort is made to protect confidentiality.

There are very few potential risks to participation in the fMRI scans. 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. Some participants 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.

To manage side effects and adverse events:

- The treatment visit window can be shortened to as little as three days if there is non-response at any dose of either medication or placebo

- We will employ a version of the MTA (Multimodal Treatment Study of Children with ADHD) ASAP (i.e., Adjunct Services, Attrition Prevention) manual to manage crisis situations. 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.
- We will offer open treatment after completion of the randomized trial, beginning with study drug but extending to the use of any treatment approach that seems indicated
- We will encourage subjects to discontinue the trial if it is not in their best interest to remain as participants.

- There are no risks involved to participants in combining these data sets.

7) Provisions for Research Related Injury

If a subject experiences a research related injury they will be asked to contact the Principal Investigators immediately. During the consent process, the guardian will be told medical care will be provided in cases where there is a research related injury. Generally, this medical care will be billed to the participant or the participant's health care insurance. In some cases, the costs of this care may be paid by someone else

8) Potential Benefits to Subjects

Participants will receive a comprehensive evaluation for ADHD and other disruptive behavior disorders, and will also be assessed for frequently occurring comorbid disorders. Participants will also receive a carefully titrated medication trial utilizing one of two commonly prescribed medications (OROS MPH or ATX), at no cost. Families may receive additional information about their child's health status from the physical examination or urine toxicology test performed as part of the study. The youth may benefit from the examinations and evaluations in this study, although they are not specifically administered for benefit, but as a precaution.

OROS MPH and ATX have both been shown to be effective in the treatment of ADHD, and are approved by the FDA for this purpose. Since the youth treated with these medications will have ADHD, they are expected to show improvement in these symptoms. As response is not 100%, not all children and adolescents with ADHD will improve during the randomized clinical trial. However, there is an open treatment period following the trial which will provide medication stabilization prior to referral to a community provider.

Parents and youth are asked to rate their satisfaction with the study medication as part of the trial, and have an opportunity to continue with the medication after the

trial. In addition, non-responders or non-toleraters of one treatment will have an opportunity for treatment with other agents during the open treatment period.

Information obtained from this study may benefit patients in the future. Thus, these data are potentially of vital importance to patients, families and clinicians in treatment selection, and identifying the neurobiological underpinnings of successful treatment.

There is neither potential benefit or harm to participants in combining the data sets, but there is potential benefit to the field and to others with the ADHD diagnosis from conducting the additional well-powered analyses proposed here.

9) Provisions to Protect the Privacy Interests of Subjects

Steps to be taken to protect participant privacy interests include conducting all study procedures in private offices with the research staff. Participants will be asked to provide a preferred method of contact e.g. phone or email. Information that is deemed sensitive or private will only be disclosed to the participant,members of the study team, or to appropriate sources inside the Mount Sinai Health System for purposes of arranging clinical referrals and helping subjects obtain clinical care.

10) Economic Impact on Subjects

Subjects may incur financial burden related for travel expenses to attend study visits and for time lost from work.

There is no additional burden or financial impact of combining the data sets.

11) Payment to Subjects

This research project is funded by the NIH. Drs. Jeffrey Newcorn (Co-PI) and Kurt Schulz (Co-PI) will be responsible for the budget management of the grant. Parents of participants will be compensated $25 for each weekly medication visits for up to 8 visits (total of up to $200 per child with ADHD) and $50 at each scan visit to help cover cost of transportation and inconvenience for weekly visits. The participant will receive $50.00 for each scan visit (total of $100 per scan/ $200 per family). In addition, parents will receive $100 for their time and effort spent during the screening process (total of $100 per family). Maximum reimbursement for a family of a child with ADHD is $500. Maximum reimbursement for a family of a healthy child without ADHD is $300.

There is no additional payment to subjects for inclusion in the combined data set.

12) Consent Process

Consent forms will be sent to the parents of potential participants prior to the study. This allows time for the parent to read through the consent carefully before the initial screening evaluation appointment. Consent will be obtained on the day of the evaluation in a private medical office (room 5-E) in 19 East 98th Street, or similarly private offices at a referring site (ex., the OPD clinic at St. Lukes). When participants arrive at MSSM for the evaluation, the principal investigator (PI) or one of the delegates will give a thorough description of the project to them, and will answer any questions they might have about the study. The SOP HRP-090 Informed Consent Process for Research will be followed and provide guidance regarding who may sign consent. In keeping with policy 3.4.2, we will obtain consent from both parents when both parents are reasonably available. It is our experience that both parents are rarely available to consent, due to divorce, work schedules, or other circumstances. Therefore, we expect the majority of participants to have consents signed by one parent or legally authorized representatives (LAR). We will accept consent from biological and adoptive parents, and LAR's (i.e., grandparents who are legal guardians). Our guidance comes from the IRB HRP-013 form, which defines '"legally authorized representative" as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research'. Additional guidance comes from policy 3.1.1.1 and 3.3 of the HRP-013.

We will share results of positive pregnancy and drug tests with parents when there is compelling social, medical or other need to share with the parents. This will be made explicit at assent, and will be documented.

To assist individuals who fail the prescreening interview in finding appropriate care, we will offer to share their contact information and evaluation status with our referral sources. We will only share this information for clinical referral purposes.

There is no additional consent involved in combining the data sets.

13) Process to Document Consent in Writing

After a thorough description of the research including the risks and benefits and the alternatives to participation, parents of the participants will be asked to sign the consent form. The witness will sign and date the "Certification of Assent of Minor" to document that the child freely assented to participate.

14) Vulnerable Populations

Include	*Exclude*	*Vulnerable Population Type*

	x	*Adults unable to consent*
x		*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
	x	*Pregnant women*
	x	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

NA

16) Community-Based Participatory Research

NA

17) Sharing of Results with Subjects

With appropriate authorization, parents may access results that are relevant to their children's ongoing clinical care. Results of assessments that are done only for study purposes (e.g. fMRI scan, genetic analysis, and behavioral data), and/or that are not useful for ongoing clinical care are not shared with the patients. Upon completion of the protocol, at the discretion of the PIs, participants may also receive either a letter to provide to their follow-up care provider or the patient may authorize the study team to provide information about the participant's treatment directly to the care provider.

18) IRB Review History

This project was approved on 7/3/12 and was re-approved on 8/10/12 after receipt of funding. This study has been approved at annual reviews since its inception. It is currently approved until 4/30/2017

19) Control of Drugs, Biologics, or Devices

Drug is purchased through the IDS and dispensed by the Mount Sinai research pharmacy. For drug accountability, bottles will be returned to the study team at each

participant visit. In the event that they cannot be returned immediately to the pharmacy, the returned drug will be held in a locked safe that meets and exceeds DEA standards for storage of a Class II drug. This safe is located in the Mount Sinai School of Medicine and belongs to the PIs.