Title: An fMRI Study of Stimulant vs. Non-Stimulant Treatment of ADHD

NCT Number: NCT02259517

Document Date: July 10, 2020

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

July 10, 2020

TO: Dr. Jonathan Posner

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE: CONTINUATION[1,2,3]**

Your protocol **#6961** entitled **Imaging stimulant vs. non-stimulant treatment of ADHD** (version date 07-10-2020) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **July 10, 2020 to July 6, 2021.** (Reviewed by the Full Board on 06-15-2020.)

Consent requirements:

□ Not applicable:

√ Signature by the person(s) obtaining consent is required to document the consent process.

□ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No □ Yes

Field Monitoring Requirements: √ Routine □ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**
√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**
√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**
√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

[1] This protocol continuation has been approved under federal regulation §46.404: Research no greater than minimal risk to children.

[2] This protocol continuation has been approved with the modifications submitted on 05-01-2020.

[3] Please note, only remote procedures may be conducted at this time. All in-person procedures are on hold until further notice, due to COVID-19 guidance. Please contact your Division Chief to discuss your specific protocol plan and contact the IRB prior to commencing any in-person procedures.

CC: RFMH Business Office (Shire, Inc. (PI: Posner); American Academy of Child and Adolescent Psychiatry (PI: Bernanke))

ENC: Assent Forms and Parent Permission Forms (v. 06-29-20), Cover Sheets, Teacher Contact Permission, Ads, Phone Script, MRI Letters, HIPAA form

EN/AHW/Scr

Protocol Title:
Imaging stimulant vs. non-stimulant treatment of ADHD

Version Date:
07/10/2020

Protocol Number:
6961

First Approval:
09/16/2014

Clinic:
Child Imaging Studies

Expiration Date:
07/06/2021

Contact Principal Investigator:
Jonathan Posner, MD
Email: posnerj@nyspi.columbia.edu
Telephone: 646-774-5735

Research Chief:
Jeremy Veenstra-VanderWeele

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation with modifications

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Child Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Brain Imaging

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
not applicable

Amendment

Describe the change(s) being made

1. We have edited the contact information on the following previously-approved recruitment materials:

- ADHD Brochure
- ADDitude Ad
- ADHD Electronic Ad
- IVY HC Flyer
- IVY Parent Recruitment Letter (uploaded in "additional documents" section)
- Metro Newspaper Advertisement (uploaded in "additional documents" section)

2. We have removed the following former employees from *Persons who are designated to discuss and document consent*:

- Jiook Cha
- Isabel Ghisolfi
- Sarah Ximena Rojas

Provide the rationale for the change(s)

1. Isabel Ghisolfi is no longer a Research Assistant in the Posner Lab, so we are replacing her contact information with that of Susie Hong, a Project Coordinator in the Posner Lab.

2. Dr. Cha, Isabel Ghisolfi and Sarah Ximena Rojas are former employees who are no longer working in the Posner Lab, and as such should no longer be listed as persons who are designated to discuss and document consent.

Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
The proposed changes do not alter or affect risks/benefits to subjects.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
The proposed changes do not require a modification to the Consent Form.

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

Our experience thus far has been very positive. We have had no adverse events. The treatment portion of the study with stimulants and non-stimulants is well-established, and our experience is consistent with this. The medications we are prescribing are FDA-approved for the treatment of ADHD in children as young as 6 years old, and we carefully titrate and monitor the dosage over the course of the study. The other components of the study (MRI scanning & psychiatric/cognitive assessment) confer minimal risks and have been well-tolerated by participants and their families.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
160
Total number of participants enrolled to date
38
Number of participants who have completed the study to date
24
Have there been any significant deviations from the anticipated study recruitment, retention or completion

estimates?
No
Comments / additional information
Recruitment and enrollment are currently paused due to the COVID-19 pandemic and we expect our enrollment numbers to be impacted as a result. We intend to start recruiting and enrolling participants again as soon as research operations resume at New York State Psychiatric Institute.

Sample Demographics

Specify population
Children with ADHD
Total number of participants enrolled from this population to date
14
Specify population #2
Healthy Control Children
Total number of participants enrolled from this population to date
24
Gender, Racial and Ethnic Breakdown

Children with ADHD
Gender: 5 Female, 9 Male
Race: 6 White, 5 Black, 1 Asian/Pacific Islander, 0 American Indian/Alaskan Native, 2 Other/Unknown or Not Reported
Ethnicity: 2 Hispanic or Latino, 4 Not Hispanic or Latino , 8 Unknown or Not Reported

Healthy Control Children
Gender: 11 Female, 13 Male
Race: 5 White, 12 Black, 0 Asian/Pacific Islander, 0 American Indian/Alaskan Native, 7 Other/Unknown or Not Reported
Ethnicity: 8 Hispanic or Latino, 2 Not Hispanic or Latino, 14 Unknown or Not Reported

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
14
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
Yes
Circumstances of discontinuation:

ADHD Participants:

1. IVY_008 completed the baseline evaluation and MRI scan, but parents were not responsive when contacted by phone and email to schedule the medication screening visit.
2. IVY_012 decided to discontinue study involvement after three weeks of medication treatment under recommendation of her pediatrician after being diagnosed with hypothyroidism.
3. IVY_013 completed the baseline evaluation and MRI scan. After the MRI scan, the mother informed us that they were no longer interested in participating in the medication treatment phase of the study and therefore discontinued their participation.

HC Participants:

1. IVY_219 completed the baseline evaluation but did not show for the MRI appointment, which was scheduled on a subsequent day. Parents were not responsive when contacted by phone and email to reschedule the MRI appointment.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Medication Trial
✓ MRI
✓ Audio or Videotaping

Population

Indicate which of the following populations will be included in this research

✓ Children (to age 7)
✓ Children (ages 8-12)
✓ Children (ages 13-17)
✓ Medically and Psychiatrically Healthy Subjects

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account

The following internal accounts will be used to support the project:

1) A Columbia University gift account and endowment under Dr. Posner's name
2) An RFMH miscellaneous (unrestricted) research fund under Dr. Posner's name
3) A CU research fund awarded to Dr. Bernanke

Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study
2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Industry
Sponsor
Shire, Inc.
Is the study investigator initiated?
Yes
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No
Who is the PI of the grant/contract?
Joel Bernanke, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Other
Sponsor
American Academy of Child and Adolescent Psychiatry
Select one of the following
Single Site
Business Office

RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Children with Attention-Deficit/Hyperactivity Disorder (ADHD) are typically treated with two types of medications with differing mechanisms of action: stimulants and non-stimulants. The stimulant Vyvanse (lisdexamfetamine, LDX), and the non-stimulant Intuniv (extended-release guanfacine, GXR), are both FDA-approved treatments for ADHD in children. Clinical trials have shown that both medications are effective in reducing ADHD symptoms, although the neurobiological mechanisms by which Vyvanse and Intuniv produce these effects remain unknown. The aim of this study is to examine the mechanisms by which LDX and GXR reduce symptoms in children with ADHD. MRI scanning will be used to understand the structure and blood flow within the brains of children with ADHD treated with LDX and GXR.

A total of thirty (30) children with ADHD and ten (10) age- and sex-matched, healthy controls will be scanned at the beginning of the study. In this first part of the study, MRI findings will be compared between the groups (i.e., children with and without ADHD) to see whether brain functioning of children with ADHD differs from that of healthy children. In the second part of the study, the children with ADHD will be randomized (1:1 ratio) to receive treatment with LDX or GXR for six (6) weeks. In the first few visits of the treatment phase of the study, the study doctor may adjust the medication dose to optimize its effect. At the end of the study, the children with ADHD treated with LDX or GXR will have a second MRI scan. The findings of that second MRI scan will be compared to the first MRI scan in order to identify brain changes due to the medication. These second MRI scans will also be compared to the scans of the healthy controls.

We seek to examine whether treatment with LDX and GXR leads to changes in brain structure and function and thereby help to reduce symptoms of ADHD. Furthermore, we will examine how these two drugs differ in yielding their therapeutic effect. This may inform how specific changes in the brain may underlie improvement in the various symptoms of ADHD.

Background, Significance and Rationale

Background, Significance and Rationale
Attention deficit/hyperactivity disorder (ADHD) is associated primarily with debilitating levels of inattention, hyperactivity, and impulsivity. Psychostimulant medications such as Vyvanse (lisdexamfetamine, LDX) are the first-line treatment of ADHD; however, many children with ADHD are treated with non-stimulant medications, such as alpha-2 agonists. Extended-release guanfacine (GXR), an alpha-2 agonist, is FDA approved for the treatment of ADHD in children.

Whereas MRI studies have examined the effects of psychostimulant treatment such as LDX on the structure and function of the brain, very limited data are similarly available on GXR effects. Interestingly, whereas LDX is thought to alleviate ADHD symptoms through its effects on dopaminergic and noradrenergic pathways, alpha-2 agonists, like GXR, are specific to noradrenergic pathways.

Combining MRI with a pharmacological trial of either LDX or GXR, we aim to examine the effects these treatments, which exhibit differing mechanisms of action, on neural circuits underlying cognitive control. Our goals are to examine and compare the effects of treatment with LDX or GXR on circuit abnormalities, to test whether engagement of target neural circuits (i.e., cognitive control circuits) results in symptom reduction (i.e., reduced impulsivity), and to explore predictors of treatment response. We will examine treatment effects using multiple units of analysis (neuroimaging, clinical interviews, and self- and parent-reports).

Developing a better understanding of how existing treatments lead to symptom improvement should facilitate the development of more effective treatments with fewer side effects.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Aim: To determine and compare the changes in brain structure and function that LDX and GXR treatment produce in patients with ADHD.

Hypothesis 1a: Before treatment, ADHD participants compared with healthy controls will have (i) significantly reduced volumes in the prefrontal cortex, (ii) altered connectivity between the prefrontal cortex and basal ganglia and (iii) reduced prefrontal task-related activation (fMRI signal) on an fMRI task of impulse control.

Hypothesis 1b: Following 6 weeks of treatment with either LDX or GXR, MRI measures of the prefrontal cortex will change to become more similar to those of healthy control participants.

Exploratory Aim: To examine the concordance between the Pubertal Development Scale (Petersen et al., 1988) and the Tanner Stages and the acceptability of these measures to participants and their parents/guardians. Parent report will be collected if participants are <11 years, and self report will be collected if participants are 11 years or older.

Description of Subject Population

Sample #1

Specify subject population
Children with ADHD
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
6-17 years

Sample #2

Specify subject population
Healthy Control Children
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
6-17 years

Gender, Racial and Ethnic Breakdown

In terms of gender, we expect the majority of children with ADHD to be male (approximately 80%), which reflects the fact that ADHD is more common in boys than in girls.

In terms of ethnic breakdown, this sample will represent a wide array of racial and ethnic backgrounds that are representative of both the population in the Washington Heights area and New York City at large (e.g., 60% White, 40% Hispanic/Latino of any race, 20% Black/African American, 5% Asian, 10% other race, 5% two or more races). Additional efforts will be made to diversify the population of participants by advertising in community/neighborhood newspapers throughout New York City and surrounding areas. We will first seek IRB approval prior to releasing these advertisements.

Description of subject population

The subject populations will consist of:

- Children with ADHD
- Healthy control children, who will be matched on age and sex.

Recruitment Procedures

Describe settings where recruitment will occur

Study Recruitment Websites
Participants will be recruited through research study recruitment websites such as RecruitMe and Clinicaltrials.gov.

Flyers and Brochures
Participants will be recruited through flyers posted and/or distributed in the community. We will post flyers on bulletin boards throughout the Columbia University Medical Center Campus, as well as in community centers, laundromats, grocery stores, and public libraries in the community. Our research staff will also seek permission from various resources in the community to distribute flyers and brochures at their events, groups, classes, etc., for parents of healthy children and parents of children with ADHD.

Advertisements
Additional efforts will be made to diversify the population of participants by placing advertisements (print or digital) in community/neighborhood newspapers throughout New York City. We will advertise on websites such as Craigslist and Google, and on social media platforms such as Facebook. We will also advertise newsletters, bulletins, and other resources (print or digital) providing information and support to parents, including those with ADHD (e.g., ADDitude magazine). Besides ADDitude magazine, another one of these digital resources providing support to parents that we will advertise in is the New York Jewish Parenting Guide website. We will seek IRB approval prior to releasing these advertisements.

Mailing
A recruitment letter providing information about this research project will be sent to mental health providers and clinicians, such as pediatricians, in the NYC area. If providers are interested in assisting us with recruitment, we will send them flyers and/or pamphlets to display at their offices or distribute to families. We will first seek IRB approval of the recruitment letter prior to mailing it to providers.

We may also send out a direct mailing to families containing information about our research study. We will recruit families by sending letters to local parents/guardians (see attached Parent Recruitment Letter). Addresses for the mailing will be obtained from Alesco Data, which is a company that maintains information on households nationwide. Alesco Data provides a service allowing the user (i.e., researcher) to obtain compiled databases or "lists" of contacts by means of various selections. In this case, we would select contacts based on geographic location (e.g., zip codes in the NYC area) and demographic characteristics (e.g., approximate age of children; 6-17 years).

How and by whom will subjects be approached and/or recruited?

Families may be approached by mental health providers and clinicians who receive information about our study through mailings and e-mails. Families may receive direct mailings about our research study. Families may also be approached by our research staff directly if our staff receive permission to distribute study information at community events and groups**.**

How will the study be advertised/publicized?

Participants will be recruited through:

- Study recruitment websites
- Flyers and brochures posted/distributed in the community
- Direct mailings
- Advertisements placed in community/neighborhood newspapers
- Advertisements on web-based resources for parents, social media platforms, and other websites such as Google

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02259517

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Protocol #7096: Umbrella Screening for Brain Imaging Studies (PI: Jonathan Posner, MD)

Protocol #6573: MRI Study of Emotion and Attention (PI: Jonathan Posner, MD)

Protocol #7261R (formerly 6235): Examining the Effects of Stimulant Medication on Emotional Liability in Patients with ADHD (PI: Jonathan Posner, MD)

Protocol #7549: MRI Study of Youth with Anxiety (PI: Jiook Cha, PhD)

Children in this study may participate in and/or be recruited from Protocol #7096, which encompasses the screening procedures for this and other research studies ongoing in this laboratory. Children with ADHD in

this study may also be recruited from Protocol #6573 (e.g., if parents express interest in medication after enrollment in #6573). Children with ADHD enrolled in Protocol #7261R will only be eligible to switch into Protocol #6961 if they have dropped out of #7261R before starting medication or if they were treated with placebo.

Healthy control data may be pooled across Protocols #6573, #7261R, and this protocol because study procedures for healthy control subjects are nearly identical across all three studies. Generally, healthy controls will NOT be scanned separately for each protocol. We may also share data collected from children with ADHD under Protocols #6573 and 7261R with data collected in this protocol.

Healthy control participants and participants with possible ADHD may be recruited from Protocol #7549 into this protocol. To minimize participant burden, we may share de-identified data collected under Protocol #7549 with this protocol, and vice versa. For example, we may share information collected as part of the lifetime diagnostic interview between the two protocols so that participants do not need to repeat this lengthy assessment and can instead provide an update on their mental health. Otherwise, assessment and MRI scanning procedures differ between this protocol and Protocol #7549; therefore healthy control participants will be assessed and scanned separately for each of these protocols.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Children with ADHD
Create or insert table to describe the inclusion criteria and methods to ascertain them

ADHD Participants	Methods of Ascertainment
1. The participant satisfies DSM-5 criteria for a primary diagnosis of ADHD, any subtype.	1. K-SADS administered by research staff (BA level or higher).
2. Participants must provide assent and a legal guardian must provide consent.	Interview, Staff Doctors
3. The participant is male or female 6 - 17 years of age and in good physical health.	Interview, Staff Doctors
4. Girls of childbearing potential must have a negative urine pregnancy test and must be using adequate contraception.	Urine pregnancy test performed by Study Staff; Interview, Staff Doctors
5. English Speaking.	Telephone Screening Questionnaire

Create or insert table to describe the exclusion criteria and methods to ascertain them

ADHD Participants	Methods of Ascertainment
1. The potential participant has a comorbid Axis I psychiatric diagnosis or other symptomatic manifestations that, in the opinion of the examining physician, will contraindicate LDX or GXR treatment or confound safety assessments.	Medical history by Staff Doctors
2. The potential participant meets DSM-5 criteria for active substance abuse and/or dependence.	K-SADS, interview by Staff Doctor
3. The potential participant is currently taking, or has taken within the past 4 months, a psychotropic medication.	Medical history by Staff Doctors
4. The potential participant has a documented allergy or intolerance to LDX or GXR products.	Medical history by Staff Doctors
5. The subject has a medical condition or family history of a medical condition (e.g., cardiovascular disease) that may interfere with study participation, or for which treatment with LDX or GXR may pose a risk to the subject.	Medical history by Staff Doctors
6. The potential participant is pregnant or lactating.	Medical history performed by Staff Doctors; Urine pregnancy test performed by Study Staff
7. The potential participant is actively suicidal * *If a participant is deemed to be actively suicidal, appropriate measures will be taken which may include escorting the participant to the emergency room and/or consulting with the participant's referring clinician.	Medical history performed by Staff doctors. Columbia Suicide Severity Rating Scale (C-SSRS) administered by Staff Doctor.
8. MRI contraindications (e.g., irremovable metal on the body, pacemaker, braces, etc.)	MRI Safety Questionnaire. Administered by study staff.
9. Full Scale IQ < 70.	WASI. Administered by study staff (BA level or higher).
10. History of seizure (except febrile seizure)	Medical history by

	Staff Doctors

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Healthy Control Children
Create or insert table to describe the inclusion criteria and methods to ascertain them

Healthy Controls	Methods of Ascertainment
1. The participant does not meet criteria for a DSM-5 disorder.	K-SADS administered by research staff (BA level or higher)
2. Participants must provide assent and a legal guardian must provide consent.	Interview by research staff (BA level or higher)
3. The participant is male or female 6 - 17 years of age	Interview by research staff.
4. Girls of childbearing potential must have a negative urine pregnancy test.	Urine pregnancy test performed by Study Staff.
5. English Speaking.	Telephone Screening Questionnaire

Create or insert table to describe the exclusion criteria and methods to ascertain them

Healthy Controls	Methods of Ascertainment
1. The potential participant meets DSM-5 criteria for active substance abuse and/or dependence	K-SADS administered by research staff (BA level or higher)
2. The potential participant is currently taking a psychotropic medication.	Telephone Screening Questionnaire
3. The potential participant has a history of a serious medical illness.	Telephone Screening Questionnaire
4. The potential participant is pregnant or lactating.	Medical history performed by Staff Doctors; urine pregnancy test performed by Study Staff
5. MRI contraindications (e.g., irremovable metal on the body,	MRI Safety Questionnaire

pacemaker, braces, etc.).	
6. Full Scale IQ <70.	WASI, administered by study staff (BA level or higher)
7. History of seizure (excluding febrile seizures).	Medical history performed by Staff Doctors

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
Yes
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process

For all participants, the screening process will begin with a brief telephone interview with the parent/guardian of the prospective participant. Before conducting the telephone interview, research staff will obtain verbal consent from the parent/guardian and document it in the screening packet or electronic record if the responses to the telephone interview are being entered directly into an electronic database.

For participants recruited from Protocol #7096:
If the information provided by the parent/guardian during the telephone screening does not exclude the child from participating, the family will be scheduled for an in-person screening evaluation. At the beginning of the screening evaluation, a member of the research team who is knowledgeable about all aspects of the screening evaluation will consent the parent/guardian. Research staff will verbally explain the nature of the screening evaluation, including the potential risks and benefits, to the parent/guardian. The parent/guardian will then be asked to read the appropriate informed consent form, and research staff will answer any questions the parent/guardian might have. If the parent/guardian understands and agrees to the requirements of the screening evaluation, research staff will obtain informed consent by having the parent/guardian sign the consent form.

At the beginning of the screening evaluation, a research staff member will also assent the child or adolescent participant. Research staff will explain the screening evaluation procedures, including associated risks and benefits, in age-appropriate language that is understandable to the participant. If the child is 8 years of age or older, he/she will be given an assent form to read. The participant will have the opportunity to ask questions about the screening evaluation and the assent form. Once the research staff member feels confident that the participant understands and agrees to the key points of the assent form, written assent will be obtained if the participant is 8 years of age or older. Otherwise, verbal assent will be obtained by research staff and documented in a progress note.

Describe Study Consent Procedures

Only a study doctor (M.D.) will consent the parent/guardian if the participant belongs to the "Children with ADHD" group. A non-physician may consent the parent/guardian if the participant is in the "Healthy Control Children" group. Non-physicians include research staff members (Bachelor's degree or equivalent) who are trained in human subjects research and knowledgeable about all aspects of the study.

At the beginning of the baseline evaluation, the nature of the research protocol, including the associated risks and benefits, will be explained verbally to the parent/guardian by the designated research staff member. Research staff will ask the parent/guardian to read a parental permission form and answer any questions the parent/guardian might have. Once research staff feels confident that the parent/guardian is comfortable with the requirements of the study, research staff will obtain informed consent from the parent/guardian by having him/her sign the consent form.

For children with ADHD, research staff will also obtain consent from the parent/guardian to contact the child's teacher in order to obtain information about the child's behavior at school.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
We are requesting a waiver of consent for the telephone screening.
Explain why your research can not be practicably carried out without the waiver or alteration

We conduct the telephone screening with parents/guardians in order to determine if participants meet basic inclusion/exclusion criteria before scheduling families to come in for an in-person evaluation. Consenting parents/guardians over the phone or in person prior to the telephone screening could significantly delay screening procedures and pose a significant burden to participants and their families, particularly if participants are ultimately ineligible for the study.

Describe whether and how subjects will be provided with additional pertinent information after participation
Following the telephone screening, we will inform parents/guardians if their children are eligible to partake

in the research study based on the information they provided. If so, we will schedule families for a baseline evaluation and MRI. If participants are ineligible and would like a referral for evaluation or treatment, we will help their parents/guardians identify mental health resources in their area.

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded

Only a study doctor (M.D.) will assent the participant if he or she belongs to the "Children with ADHD" group. Non-physicians may assent the participant if he or she belongs to the "Healthy Control Children" group. Non-physicians include research staff members (Bachelor's degree or equivalent) who are trained in human subjects research and laboratory procedures.

At the beginning of the baseline visit, the designated research staff member will explain the study procedures, including associated risks and benefits, in age-appropriate language that is understandable to the participant. If the participant is 8 years of age or older, he/she will also be asked to read the assent form. The participant will have the opportunity to ask questions about the study procedures and the contents of the assent form. Once the designated research staff member feels confident that the participant understands and agrees to the key points of the assent form, written assent will be obtained if the participant is 8 years of age or older. If the participant is 7 years of age or younger, verbal assent will be obtained by research staff and documented in a progress note.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Hong, Susie
Lugo-Candelas, Claudia
Pieper, Sarah
Posner, Jonathan, MD
Raffanello, Elizabeth
Semanek, David
Type in the name(s) not found in the above list
Bernanke, Joel, MD

Study Procedures

Describe the procedures required for this study
The term "study doctor" refers to the physicians listed under *Persons designated to discuss and document consent*.

Telephone Screening

Research staff will conduct a brief telephone interview with parents/guardians of prospective child participants. As described in the Consent Procedures section of the PSF, the research staff member will obtain and document verbal consent for the telephone screening before administering it. The telephone screening interview includes a set of questions regarding key inclusion/exclusion criteria (e.g., child's age, MRI contraindications, psychiatric history, physical health history), and a symptom rating scale to screen for ADHD. Research staff may enter responses to the telephone screening directly into an electronic database as they are administering the questionnaire. In these cases, research staff will document that verbal consent was obtained by marking a box or writing a comment in participants' electronic record.

Telephone screening will be conducted through Protocol #7096, which is the screening protocol for research studies ongoing in the PI's lab. In addition to administering the version of the telephone screening that has been approved as part of the screening protocol, our staff will administer the ADHD Rating Scale-5 over the phone to parents/guardians in order to assess ADHD symptoms.

Baseline Evaluation and MRI Scan

If participants meet the study inclusion/exclusion criteria based on the telephone screening, they will be scheduled for a baseline evaluation at our offices at NYSPI, where all other study procedures will take place. The baseline visit will be completed by all participants (ADHD and healthy control) and involves neuropsychological testing, diagnostic assessments, assessment of pregnancy and use of contraceptives in female participants of childbearing potential, and an MRI scan.

Participants recruited from Protocol #7096 will have already completed the neuropsychological testing and diagnostic assessments as part of the in-person screening evaluation for ongoing brain imaging studies. If participants are eligible, and parents and participants consent/assent to this study (#6961), participants will complete the rest of the baseline visit on the same day as the in-person screening evaluation or shortly thereafter, depending on participant/parent preference, availability, potential for fatigue (e.g., participant's young age), etc.

1. Neuropsychological Testing

All participants will undergo neuropsychological testing that includes measures of impulse control and working memory. A measure of intelligence will also be collected in order to ascertain whether the participant has a minimum level of intellectual functioning (as determined by an estimated IQ of 70 or above) at study entry. The tests will be conducted by a trained member of the research staff (Bachelor’s degree or equivalent) and take between 1 and 2 hours to complete.

Participant sessions of neuropsychological testing will be randomly selected for audio or video recording in order to review that they are being administered properly. These recordings will be deleted within 4 months of when they were made.

2. Diagnostic Assessments

Parents/guardians and participants will undergo structured diagnostic interviews that will ask questions about participants' current and past medical and psychiatric history. In addition, parents/guardians and participants will be administered symptom rating scales that ask additional questions about participants' psychiatric symptoms, behavior, thoughts, and emotions. (Please see the *Assessment Instruments* section of the PSF for a complete listing of these measures and their time requirements.)

These diagnostic assessments will be administered by a trained member of the research staff (Bachelor's degree or equivalent) and will take between 2 and 3 hours to complete.

3. MRI Scan

Prior to the MRI, we ask parents/guardians to complete the NYSPI Department of Psychiatry MRI Metal Screening Questionnaire in order to confirm that participants do not have any MRI contraindications. Participants will be asked to remove any jewelry, watches, or other metal before the MRI scan. A metal detector will be used in addition to the screener in order to help confirm that participants do not have any metal on or in their body. If any MRI contraindications (e.g., metallic implants) are detected, participants will be withdrawn from the study.

All girls who are post-menarche will be required to take a urine pregnancy test prior to the MRI scan in order to confirm that they are not pregnant. The test will be conducted on-site and will be paid for by the study. Participants will also have the option of having a confidential pregnancy test outside of the clinic. For pregnancy tests conducted on-site, trained research staff (Bachelor's degree or equivalent) will collect urine samples and conduct pregnancy tests on the day of the MRI scan. Girls will only be permitted to enter the MRI control room and magnet room if their pregnancy test is negative. In the unlikely event of a positive pregnancy test, a trained clinician (i.e., Master's level or higher clinician) will be called to come and discuss the pregnancy test results with the participant and her parent/guardian at that time. If a parent is not present, the clinician will call the parent and/or arrange for the parent to come to NYSPI in order to discuss the results. Whether the parent and the child are told the results of the pregnancy test together or separately will be determined on a case-by-case basis by the clinician in consultation with Dr. Posner and other senior staff based on all available data on the family. The clinician will provide appropriate information and referrals and encourage the participant to consult with their primary physician or with a family planning clinic.

The MRI scan will be conducted on the 3-Tesla scanner at NYSPI. An accredited MR technologist and a trained member of our research staff (Bachelor's degree or equivalent) will carry out the MRI procedure. The MRI will last 60 to 90 minutes include anatomical, resting, diffusion tensor imaging (DTI), arterial-spin labeling (ASL), and functional pulse sequences. The functional tasks will be developmentally appropriate with respect to instructions, stimuli, etc.

Trial of Lisdexamfetamine (LDX) or Extended-Release Guanfacine (GXR)

After completing the baseline visit, ADHD participants will begin treatment with either LDX or GXR. The treatment phase of the study will last 6 weeks, during which time participants will meet regularly with the study doctor (approximately once a week). We will offer these clinic appointments during after school hours.

The study doctor will titrate each participant to his/her optimal dose of the medication, which will maximize clinical benefit and minimize negative effects (e.g., tics). Side effects and adverse events including tics will be assessed at weekly visits over the course of treatment. All side effects or adverse events will receive timely review by the study doctors to determine if they might necessitate withdrawal from treatment.

The study design for the medication trial is outlined in the following paragraphs:

1. Medication Screening Visit

The treatment screening visit will be conducted on the same day as the baseline MRI scan or shortly thereafter. During the screening visit, the study doctor will review the treatment procedures with participants and conduct a medical history. The study doctor will also conduct a physical exam and/or urine toxicology screening if he feels that these procedures are indicated based on the medical history obtained. In addition, the study doctor will assign the participant a Clinical Global Impression – Severity (CGI-S) score. The CGI-S is a global evaluation of patient's functioning and rates severity on a 7-point scale ranging from 1 to 7 (1 = normal, not at all ill; 7 = among the most extremely ill patients).

- For ADHD participants with a history of tic disorder: Based on the information gathered from the medical history and the psychological assessments during the initial visit(s), the study doctor will carefully weigh the risks and the benefits of LDX treatment with the parent/guardian of the child participant. The decision to randomize the participant or to remove him/her from the study will depend on the study doctor's clinical judgment and the preferences of the parent/guardian. The study doctor will follow the same clinical practice guidelines for evaluating and treating co-occurring ADHD and tic disorder as doctors in the community. If the study doctor and parent/guardian agree that the benefits of potential treatment with LDX outweigh the risks, then the participant will proceed to the randomization procedures outlined below.

- For female ADHD participants who have had their first period: Female ADHD participants who have had their first period and who are sexually active will need to: (1) be using contraception prior to beginning treatment, and (2) agree to continue using contraception throughout the course of treatment in order to participate in the study. The study doctor will talk to female participants who have had their first period about ways to prevent pregnancy, the potential risks of the study medications on pregnancy (as part of consent/assent), as well as the limitations of urine pregnancy testing. Participants and their parents/guardians will be advised to notify the researcher immediately should they suspect that the participant is pregnant. If a participant is suspected to be pregnant, we will perform another pregnancy test to determine if she should continue the study. In case of pregnancy, the participant will discontinue the study early and we will provide assistance with obstetrical follow-up.

2. Randomization Procedures

Eligible ADHD participants will be randomized to treatment with LDX or GXR using a 1:1 ratio. Participants, research staff, and the study doctor will NOT be blinded to treatment.

3. Medication Management

Following randomization, participants will be taken through a medication management protocol over the subsequent 6 weeks. This protocol will begin with 4 weeks of medication titration, which will be followed by 2 weeks of medication maintenance. Titration will help the study doctor determine the minimum dose of medication necessary to achieve treatment response.

ADHD participants will be seen approximately once a week during the treatment phase of the study. At each visit, the study doctor will assess clinical response including symptom change, side effects, adverse events, and changes in functional impairment. Symptom change will be documented using the Clinical Global Impression-Improvement (CGI-I), which is a clinician-rated global measure of a participant's improvement over time, relative to the conditions observed at baseline (i.e., CGI-S). Like the CGI-S (administered at the Medication Screening Visit), the CGI-I is rated on a 7-point scale (1 = very much improved; 7 = very much worse). Side effects and adverse events will receive timely review by the study doctor, who will determine the appropriate response (e.g., adjust dose, discontinue participant early from study). Participants and their parents/guardians will be encouraged to call the study doctor at any time to report side effects or adverse events. They do not have to wait until the next scheduled treatment visit in order to inform the doctor of side effects or adverse events.

The study doctor will prescribe sufficient medication to provide once daily dosing until the next scheduled visit. Although we will make every effort to see subjects weekly, in our experience, this may prove difficult due to cancellations, sickness, holidays, etc. To prevent a gap in treatment, the study doctor may dispense up to 30 days of medication at his/her discretion.

- Titration of LDX: The treating physician will dose LDX to optimize clinical response. Titration will begin at 30 mg and will advance through the dosage range (30 mg, 50 mg, or 70 mg) to find the best response that provides no more than mild adverse events. Treatment response will be defined as a clinician-rated CGI-I score ≤ 2 (Improved or Very Much Improved) with no more than mild associated adverse events based on a clinical review of side effects. Flexibility in the dosing will be up to the treating physician as long as the dosing does not go outside of the FDA approved guidelines of 20 - 70 mg daily.

- Titration of GXR: The treating physician will dose GXR to optimize clinical response. Titration will begin at 1 mg and will advance through the dosage range (1 - 4 mg) to find the best response that provides no more than mild adverse events. pastingTreatment response will be defined as a clinician-rated CGI-I score ≤ 2 (Improved or Very Much Improved) with no more than mild associated adverse events based on a clinical review of side effects. For children under 25 kg/55 lbs, the dose of GXR will not exceed 1 mg per day. The treating clinician will monitor heart rate and blood pressure to ensure that cardiovascular risk is minimized. Flexibility in the dosing will be up to the treating physician as long as the dosing does not go outside of the FDA approved guidelines of 1 - 4 mg daily.

- Concomitant Medication: The treating physician will review any potential concomitant medications, and make recommendations as clinically indicated. For example, GXR doses may be adjusted when used concomitantly with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin) or inducers (e.g., avasimibe, carbamazepine). In clinical practice, melatonin is often used to alleviate insomnia related to ADHD medications like LDX. The treating physician will have the option of recommending melatonin 1-6 mg nightly as needed for insomnia.

See Criteria for Early Discontinuation

Follow Up Evaluation and MRI Scan

After completing the medication trial, children with ADHD will be scheduled for a follow-up evaluation. The follow-up evaluation will be similar to the baseline evaluation but shorter in length. The second MRI scan will be identical to the first MRI scan.

1. Neuropsychological Testing: We will repeat all neuropsychological tests with the exception of the measure of intelligence, which is not expected to change during the study period.

2. Diagnostic Assessments: Likewise, we will repeat all diagnostic assessments with the exception of the diagnostic interview.

3. Second MRI Scan: The procedures for the second MRI scan will be identical to the first MRI scan. In summary, parents/guardians will be asked to fill out the MRI Metal Screening Questionnaire to confirm that participants do not have any MRI contraindications. Parents/guardians will be reminded to have their children dress in comfortable clothing without any metal on them. Before the MRI scan, participants will be asked to remove any jewelry, watches, etc. A metal detector will be used to confirm that participants do not have any metal on their body. Female participants who have had their first period will take a urine pregnancy test to confirm they are not pregnant. Participants with MRI contraindications will not undergo the second MRI scan.

Like the first MRI scan, the second MRI scan will last 60 to 90 minutes include anatomical, resting, diffusion tensor imaging (DTI), arterial-spin labeling (ASL), and functional pulse sequences. The functional tasks will be developmentally appropriate with respect to instructions, stimuli, etc.

Follow Up Treatment

All ADHD participants will be followed free-of-cost by the study team until an appropriate referral is secured. We will supply participants with either LDX or GXR, matching the treatment received during the clinical trial, free-of-cost for one month. After the first month, parents/guardians will have to pay for the medication. To secure timely referrals, the study team will begin arranging for follow-up care as soon as possible after ADHD participants begin the study.

Future Research

After completing the study, we may re-contact parents/guardians in order to ask them and/or their child who participated in the study about completing additional assessments. The assessments would be an extension of the baseline (healthy control participants) or follow-up evaluation (ADHD participants). For example, we may ask parents/guardians and participants to complete an additional rating scale or brief neuropsychological assessment. Only assessments listed in "Assessment Instruments" would be administered.

Likewise, after completing the study, we may contact parents/guardians about participation in future research such as ongoing or new studies in the lab. Participants and their parents/guardians will not be required to partake in future research and may decline participation when contact. Parents/guardians may withdraw their permission to be contacted at any time by contacting the research team.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Treatment Response: The study doctor will complete the Clinical Global Impression-Improvement (CGI-I) scale during weekly visits with participants to track improvement in symptoms over time. The CGI-I is rated on a 7-point scale ranging from 1 to 7 (1 = very much improved; 7 = very much worse). Any occurrence of a CGI-I score of 6 or higher (much worse or very much worse) will trigger a clinical evaluation. Based on clinical judgment, the study doctor will determine whether the patient should be discontinued from the study.

Medication Compliance: Treatment compliance will be monitored by review of subject diaries and pill counts at each visit. Compliance rates will be recorded at each visit. Participants who are non-compliant with the prescribed treatment, defined as taking < 70% of the assigned medication, will be counseled and, after repeated instances of noncompliance, will be subject to discontinuation from this study at the discretion of the investigators.

Pregnancy: LDX and GXR are not considered safe during pregnancy or breastfeeding because there is concern about causing permanent damage to a developing fetus or young infant (e.g., birth defects, or problems that emerge during infancy or childhood). Participants and their parents/guardians will be advised to notify the researcher immediately should they suspect participant pregnancy. In case of suspected pregnancy, we will perform a pregnancy test and the participant will be discontinued early from the study. We will not provide free medication treatment if a participant is pregnant. Instead, we will provide assistance with obstetrical and mental health follow-up.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Not applicable

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

1. Parent Informant

Measure	Time to Administer
Subject Profile Questionnaire - Child Version	10 minutes
Hollingshead Socioeconomic Status (SES) Index	2 minutes
Kiddie Schedule for Schizophrenia and Affective Disorders (K-SADS)	40 minutes
Child Behavior Checklist (CBCL)	10 minutes
Conners 3 Parent-Report	5 minutes
ADHD Rating Scale-5	2 minutes
Emotion Regulation Checklist (ERC)	5 minutes
Social Responsiveness Scale, Second Edition (SRS-2)	5 minutes
Family Environment Scale (FES)	5 minutes
Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) Parent Questionnaire	10-15 minutes
Affective Reactivity Index parent (ARI-p) form	2 minutes
Children's Affective Lability Scale (CALS)	5 minutes
Pubertal Development Scale (PDS) - if child participant is 6-10 years old	2 minutes

2. Self-Informant

Measure	Time to Administer
Edinburgh Handedness Inventory	2 minutes
Kiddie Schedule for Schizophrenia and Affective Disorders (K-SADS)	40 minutes
Children's Depression Inventory, Second Edition (CDI-2)	10 minutes
Revised Children's Manifestation Anxiety Scale, Second Edition (RCMAS-2)	5 minutes

UPPS-P Impulsive Behavior Scale for Children	10 minutes
11-17 year olds only:	
Affective Reactivity Index self-report (ARI-s) form	2 minutes
Tanner Stages - Sexual Maturity*	2 minutes
Pubertal Development Scale (PDS)	2 minutes

*Parent will complete this form for children < 11 years of age

3. Neuropsychological Testing

Measure	Time to Administer
Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)	40 minutes
Computerized Tasks:	
Kiddie Continuous Performance Test, Second Edition (K-CPT-2; 6-7 years old) or Conners CPT, Third Edition (CPT 3; 8 years and older)	20 minutes
NIH Toolbox Flanker Inhibitory Control and Attention Task and Dimensional Change Card Sort Test	20 minutes

5. Take-home questionnaires (for Teacher)

Measure	Time to Complete
Teacher ADHD Rating Scale (e.g., BRIEF Teacher Form)	10 minutes

*These questionnaires will be given to the participant's parent(s) with addressed and stamped envelopes. We will request that the parent give these forms to one of the participant's teachers and that the completed forms are then mailed back.

6. Other Clinical Measures

Measure	Time to Administer
Cardiac Risk Checklist	5 minutes
Clinical Global Impression-Improvement (CGI-I)	5 minutes
Clinical Global Impression–Severity (CGI-S)	5 minutes
Children's Global Assessment Scale (C-GAS)	5 minutes
Columbia Suicide Severity Rating Scale (C-SSRS)	5 minutes

Pittsburgh Side Effects Rating Scale (PSERS)	2 minutes

* The total time to fill out the list of measures noted above will be approximately 3 hours

7. Description of Nonstandard Measures

Measure Description and Rationale

Subject Profile Questionnaire - Child Version
This is a medical and developmental report filled out by the participant's parent (please find attached).

Cardiac Risk Checklist is filled out by the study physician, documenting potential risk for sudden death due to cardiomyopathy. It includes items about known history of structural heart defect, history of fainting during exercise, history of sudden death in a first degree relative, or history of syncopal episodes or seizure.

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study

All ADHD participants will be followed free-of-cost by the study team until an appropriate referral is secured. We will supply GXR or LDX to ADHD participants free-of-cost for one month after completing the study. The medication and dose supplied will match the treatment each participant received during the study. After the first month, families will have to pay for the medication. Should families choose to continue treating their child's ADHD with GXR, the average cost of the medication is about $156 per 1-month supply. Should families choose to continue treating their child's ADHD with LDX, the average cost of the medication is about $230 per 1-month supply. Participants who become pregnant during the course of the study will be followed in the same way, except that free medication will not be provided (see Criteria for Early Discontinuation).

Clinical Treatment Alternatives

Clinical treatment alternatives

According to the American Academy of Pediatrics, treatment of ADHD in elementary school-aged children should include: (1) an FDA-approved medication for ADHD, and/or (2) evidence-based parent and/or teacher-based behavior therapy. With respect to medication treatment, there is strong evidence supporting the effectiveness of stimulant medications and sufficient but less strong evidence for medications such as atomexetine, GXR, and extended-release clonidine. For adolescents, treatment should include an FDA-approved medication for ADHD with the assent of the adolescent and, preferably, behavior therapy.

Thus, alternative clinical treatments include other FDA-approved stimulant and non-stimulant medications for ADHD and evidence-based behavior therapy.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

LDX Treatment: The most common adverse experiences associated with LDX include headache, abdominal pain, insomnia and anorexia. Other side effects seen with LDX include nausea, vomiting, dizziness, nervousness, hypersensitivity, pulse and blood pressure changes, palpitations, tachycardia, dyskinesia, angina, and drowsiness. In children, loss of appetite, abdominal pain, and weight loss can occur with prolonged use. Other reactions that can occur less frequently include motor tics and social withdrawal. There is some evidence that in rare cases, stimulant medication (like LDX) can worsen motor tics and Tourette's syndrome in patients with these problems. Although they are very rare, hallucinations and psychotic episodes have been reported. Stimulant medication might also lower the seizure threshold in patients with a history of seizures or patients with abnormal EEGs without seizure activity.

Additional risks include:

- Abuse Potential: LDX is classified as a Schedule II controlled substances by Federal regulation. It is well known that tolerance, extreme psychological dependence, and severe social disability may occur when these products are abused.
- Sudden Cardiac Death: Although a definitive link between the use of stimulant medications (such as LDX) and sudden cardiac death has not been established, some studies have suggested that stimulants may increase the risk of sudden cardiac death.

GXR Treatment: Serious but uncommon adverse experiences associated with guanfacine are hypotension, syncope, bradycardia, AV block, hypersensitivity, exfoliative dermatitis, seizures, and hallucinations. Other more common side effects include: somnolence, headache, fatigue, dizziness, abdominal pain, lethargy, nausea, irritability, decreased appetite, diarrhea, dry mouth, constipation, and mood fluctuations. Risks that could be encountered during the study period:

MRI: Both the FDA and the NYSPI IRB have deemed MRI scanning on the GE 3 Tesla MRI Scanner at the New York State Psychiatric Institute to be classified as a non-significant risk. While there are no known risks from short-term exposure to the MRI, MRI scanners have a strong static magnetic field that will attract any magnetic objects on or in the body, a magnetic field that varies with time which creates loud noises, and radiofrequency energy that can lead to heating in the body. Additionally, some people are uncomfortable in the MRI scanner because it is a small, enclosed space. Some people also find it uncomfortable or difficult to remain still for long periods, which is necessary to capture clear images in the MRI scanner.

Pregnancy Testing: Risks associated with pregnancy testing include fear/worry about a positive outcome, embarrassment or shame over past sexual contacts, and concern about parents' reaction should the test be positive.

Missed School: Due to the length of the baseline and follow-up appointments, children may miss some school while participating in the study.

Neuropsychological Testing: Risks encountered during neurological testing includes possible boredom, fatigue, and frustration with difficult test items.

Diagnostic Assessments: Risks associated with diagnostic interviews and other psychological assessments include fatigue, boredom, and possible emotional distress related to questions about current and past psychiatric symptoms.

Describe procedures for minimizing risks

LDX Treatment: To minimize risk, we will exclude participants with a history of seizures (except febrile), cocaine or stimulant abuse/dependence, and cardiac disease. We will also exclude participants with a family history of cardiac-related death (age < 40). The study doctor will obtain a personal and family history of heart problems from all participants. We will not obtain EKGs as a screening tool for all participants because the American Academy of Pediatrics do not recommend this measure in their statement on the use of stimulants and cardiovascular monitoring. Please refer to "Inclusion/Exclusion Criteria" for a complete listing of eligibility criteria.

For ADHD participants with a history of tic disorder, prior to initiating treatment, the study doctor will carefully review the risks and benefits of LDX with the participant or parent/guardian based on the information gathered from the medical history and the results of the psychological evaluation. The decision to randomize the participant or to remove him/her from the study will depend on the study doctor's clinical judgment and the preferences of the participant and parent. The study doctor will follow the same clinical practice guidelines for the treatment of co-occurring ADHD and tic disorder as doctors in the community. If

the study doctor and the participant and parent agree that the benefits of potential treatment with LDX outweigh the risks, then the participant will be randomized to medication or placebo. The study doctor will titrate each participant to the minimum dose necessary to achieve response. This will maximize clinical benefit and minimize negative effects (e.g., tics) of the medication. Side effects and adverse events, such as tics, will be assessed at weekly visits over the course of treatment. The participant may reach the study doctor between visits if he/she experiences an exacerbation of tics. All side effects and adverse events will receive timely review by the study doctors to determine if they necessitate withdrawal from treatment.

GXR Treatment: Children with known heart defects and other serious health conditions contraindicating treatment with guanfacine will be excluded from the study. The treating clinician will monitor heart rate and blood pressure to ensure that cardiovascular risk is kept to a minimum. For children under 25 kg or 55 lbs, the dose of GXR will not exceed 1 mg per day.

Psychiatric Emergencies: Psychiatric emergencies will be assessed as they occur during the study. For emergencies during the course of treatment, the Principal Investigator and/or a co-investigator will be available 24-hours a day, 365 days per year. All participants will be given three numbers to call, in the event of an emergency: the primary phone number of the treating clinician (i.e. the study doctor), the principal investigator's contact numbers, and the number of the NewYork-Presbyterian Hospital Emergency Room.

A related risk is that children with ADHD frequently have co-morbid psychiatric conditions and these conditions could thus also go untreated in this study. However, if a participant's overall functioning deteriorates over the course of the study (defined by CGI-I score of 6-7 for two consecutive weeks), then they will be removed from the study and referred for treatment.

MRI: Participants will be carefully screened for MRI contraindications including any magnetic objects on or in the body using the MRI Metal Screening Questionnaire and metal detection. A urine pregnancy test will be conducted with female participants who have had their first period to confirm that they are not pregnant. Participants will be encouraged to utilize the mock MRI scanner as a means of becoming accustomed to the MRI scanning environment. During the MRI, participants will be fitted with adequate ear protection to prevent harm from the loud noises generated by the scanner. Research staff and the MRI Technician will frequently communicate with participants between sequences to determine if they are tolerating the MRI scanning procedures well. Additionally, participants will be given an alarm that they can sound if they require the immediate response of research staff and the MRI technician and/or wish to end the MRI scan early.

Pregnancy Testing: Pregnancy testing associated with concerns about a positive outcome, embarrassment or shame over past sexual contacts, or worry that parents might become upset with the outcome. If the results of the pregnancy test cause the participant any distress, a trained member of the research staff will discuss the results with her, and appropriate referrals will be made. The participant will also be offered the option to have a confidential pregnancy test outside of the study clinic.

Missed School: For all study procedures, we will make every effort to minimize children missing school (e.g., scheduling during evenings, school vacations); however, this is not always possible due to the length of the baseline and follow-up visits. In community practice, it is not uncommon for child psychiatrists to

conduct initial psychiatric evaluations of children during school hours because they are often quite time consuming.

Neuropsychological Testing: Risks encountered during neuropsychological testing includes possible boredom, fatigue, and frustration. If the participant no longer wishes to continue the testing, they may stop at any time. Any adverse events that occur during testing and/or any information that warrants clinical attention (i.e., suicidal ideation, intent to harm oneself/others) will be reported immediately to Dr. Posner, and proper interventions and referrals will be made.

Diagnostic Interviews: Risks associated with diagnostic interviews include boredom, fatigue, and possible emotional distress related to questions about psychiatric symptoms and history. If the participant or parent no longer wishes to continue the interview, s/he may stop at any time. Any adverse events that occur during the interview and/or any information that warrants clinical attention (i.e. suicidal ideation, intent to harm oneself/others) will be immediately reported to Dr. Posner, and proper interventions and referrals will be made.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

Paper copies of research records will be stored in locked filing cabinets located in our offices at NYSPI. Research records, both paper and electronic, will be labeled with a unique code or ID that is randomly generated instead of personal identifying information. Paper copies of research records will contain signed consent/assent forms, participant/parent payment forms, and a copy of the completed telephone screening questionnaire, all of which contain personal identifying information.

All electronic data will be stored on our lab's secure and encrypted Network Attached Storage (NAS) that is connected to the NYSPI network and was set up by PsyIT. De-identified electronic data may be transferred to the encrypted computers or storage devices of research staff working on this study to facilitate data management, analysis, and summary of results.

For the purposes of tracking and scheduling participants, our research lab will maintain a secure electronic database containing basic information about participants such as their name, contact information, unique ID, and date of evaluation and MRI scan. The tracking database will be password-protected and stored on our lab's secure NAS. Access will be restricted to select research staff in Dr. Posner's lab (e.g., RAs involved in scheduling participants).

All electronic databases containing data, such as responses to psychodiagnostic and cognitive assessments administered pre- and post-treatment, will be de-identified and entered into a separate electronic database. Participant data will be labeled with unique IDs. Likewise, electronic data generated from computer-based tasks will also be devoid of personal identifying information and labeled with unique IDs.

The MRI Unit at NYSPI will store de-identified MRI data collected as part of this study on XNAT, a secure data archiving tool for neuroimaging research. De-identified MRI data will be uploaded onto our NAS. Only permitted research staff working on this study will have access to MRI data collected as part of this protocol.

Any presentations, publications, or other scientific reports summarizing the results of this study will NOT contain participants' personal identifying information.

There are two exceptions to confidentiality, which are listed below:

- Suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others will be reported to the appropriate authorities.
- Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits).

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
For ADHD participants, a potential direct benefit is symptom improvement as a result of taking an FDA-approved medication for the treatment of ADHD.

For all participants, a potential direct benefit is receiving a psychiatric evaluation and MRI, which could uncover mental health or physical health issues that were previously unidentified and untreated. Participants and parents will receive information and referral if the evaluation uncovers any possible issues requiring mental health or physical health care.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

Participants will not be charged for any of the study procedures, and all participants (ADHD and HC) will receive compensation for their time and effort spent partaking in the evaluation(s) (neuropsychological and psychological assessments) and MRI scan(s). Parents of ADHD participants will be compensated for completing assessments at weekly treatment visits.

- Maximum compensation to ADHD participant = $270. Maximum compensation to parent/guadian of ADHD participant = $300
- Maximum compensation to HC participant = $160

ADHD Participants

Baseline and Follow-up Evaluation and MRI: ADHD participants will be compensated $100 if they complete the baseline evaluation and MRI scan, and they will be compensated $150 if they complete the follow-up evaluation and MRI scan. Adolescent (12 years and older) participants will be paid by check, which will be sent to their home address within 2 to 4 weeks of completing the baseline or follow-up MRI. Children (11 years or younger) will be paid by gift card to a major retailer that sells toys. Child participants will be handed the gift card at the end of their baseline or follow-up MRI.

Treatment Visits: The parent/guardian of child participants will likewise receive $50 in cash at the end of each treatment visit (up to 6 visits) for a maximum of $300.

Healthy Control Participants
HC participants will receive $150 if they complete the baseline evaluation and MRI scan. For adolescent (12 years and older) participants, payment will be in the form of a check mailed to their home address within 2 to 4 weeks of completing the MRI scan. Child participants (11 years and younger) will be compensated in gift cards to a major retailer that sells children's toys.

All Participants
During the baseline and follow-up evaluations, participants may be asked to complete a Probabilistic Learning Task. We will tell the participants that they can earn up to an additional $10 in cash based on their completion and performance during the task. However, we will give them the compensation regardless of how they perform. The amount that participants earn or win during the task will be handed to them at the end of the evaluation.

If participants end the baseline or follow-up evaluation and MRI scan early, they will be paid $20 per hour of participation up to a maximum amount of $100. Adolescent participants will be paid by check, which will be mailed to their home address within 2 to 4 weeks of their baseline or follow-up visit. Child participants will be paid by gift card, which will be handed to them at the end of the evaluation or MRI scan.

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