NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

July 24, 2017

TO: RACHEL MARSH, PHD

FROM: Dr. Edward Nunes, Co-Chairman, IRB

Dr. Laurence Greenhill, Co-Chairman, IRB

SUBJECT: EXPEDITED APPROVAL OF PROTOCOL AMENDMENT

The amendment to your protocol #7006 entitled: OVERLAPPING NEURAL CIRCUITS IMPLICATED IN PEDIATRIC OCD **(updated personnel including staff and persons designated to obtain consent; updated recruitment materials to change the contact person, as per the 7/6/2017 memorandum)** has been approved by the Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board.

Please note that this does not change the IRB's cycle of review. A progress report and an application for continuing review will be required 2 months before the study's approval is due to expire: (2/22/2018).

Signed copy on file at IRB.
EN/LG/whiteda

Protocol Title:
Overlapping Neural Circuits Implicated in Pediatric OCD

Version Date:
07/24/2017

Protocol Number:
7006

First Approval:
03/25/2015

Clinic:
Child Imaging Studies

Expiration Date:
02/22/2018

Contact Principal Investigator:
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Co-Investigator(s):
Moira Rynn, MD

Research Chief:
Moira Rynn, MD

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 proposing an amendment only to an existing protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Child Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
None

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.
All investigators are affiliated with the New York Psychiatric Institute or Columbia University.

Amendment

Describe the change(s) being made
1. We would like to add Kelsey Hill, Kristin Toffey, and Juliet Jenkelowitz. They have all completed CITI training and their certificates are on file.

2. We would like to add Kelsey Hill, a research assistant who was recently hired to assist with this study, to the list of individuals designated to obtain and discuss consent.

3. We would like change the contact person on recruitment materials from Dylan Braun to Kelsey Hill.
Provide the rationale for the change(s)

1. We would like to update our list of personnel to reflect changes in staffing.

2. We would like to update our list of individuals designated to obtain and discuss consent to reflect changes in staffing.

3. We would like change the contact person on recruitment materials to reflect changes in staffing.

Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
The proposed changes will 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 will no require a modification to the Consent Form (CF).

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures
✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Psychotherapy Trial
✓ MRI

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?
No
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
Federal
Institute/Agency
NIMH
Grant Name
Overlapping Neural Circuits Implicated in Pediatric OCD
Grant Number
R21MH101441
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Funding Source #2

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
Federal
Institute/Agency

Youth Anxiety Center
Grant Name
Youth Anxiety Center
Grant Number
PC002245
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

Lay Summary of Proposed Research

This study will use magnetic resonance imaging (MRI) to assess the function and structure of overlapping frontostriatal circuits in children and adolescents with Obsessive-Compulsive Disorder (OCD) before and after a standard course of evidence based Cognitive Behavioral Therapy (CBT). The functioning of frontostriatal control systems will be assessed using the well-validated Simon task. Functioning of the dorsal striatum and ventral frontostriatal circuits that support habit learning and reward processing will be assessed using a novel fMRI paradigm directly analogous to tasks used to define the neural bases of reward-based learning systems in rodents, tailored to a virtual reality environment within the MRI scanner. This study will also assess functional and anatomical connectivity within dorsal and ventral frontostriatal circuits in the same children and adolescents, and determine whether disturbances in these overlapping circuits are associated with OCD symptom severity. Participants will also undergo an MRS scan to measure striatal Glu levels. Behavioral measures will be administered to further assess regulatory, learning and memory functions. Children and adolescents with OCD will then be offered a evidence based standard course of cognitive behavioral therapy before rescanning (along with age-and gender-matched control participants) in order to assess how these circuits may change with treatment. In addition, de-identified data may be used in the future to conduct secondary data analyses. As we learn more about the diagnoses and neurobiological mechanisms of interest in the current study, we may use these data to answer questions beyond those described in this protocol. All study procedures will be conducted on-site at the New York State Psychiatric Institute.

Background, Significance and Rationale

Background, Significance and Rationale

Obsessive-Compulsive Disorder (OCD) is characterized by intrusive thoughts, images, or impulses (i.e., obsessions) and repetitive acts performed to prevent or reduce distress (i.e., compulsions). Early-onset (i.e., pediatric) OCD is often considered a distinct OCD subtype given its greater familiality, genetic differences, comorbidity with tic disorders and ADHD, and male preponderance. Prior work suggests that OCD is characterized by dysfunction in the frontostriatal circuits (FS) that subserve inhibitory control. Dysfunction in dorsal circuits impairs regulatory control over intrusive thoughts (obsessions) and compulsive behaviors. Dysfunction in ventral circuits contributes to reward processing deficits, decreasing the rewarding relief that should result from the behaviors and enhancing urges to repeat them. Abnormal maturation of FS circuits also contributes to an over-reliance on the dorsal striatum (DS) in OCD, allowing compulsive behaviors to evolve into "habits." This study plans to examine the structure and function of these circuits in a large sample of unmedicated OCD children and adolescents. We will combine both well-validated and novel fMRI paradigms, along with measures of functional and anatomical connectivity. We will also explore measures of cortical thickness and subcortical volumes and changes in circuit-based abnormalities following treatment. All study procedures will be conducted on-site at the New York State Psychiatric Institute.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

The goal of this study is to use multimodal MRI to assess the functioning and structure of overlapping frontostriatal circuits in a large sample of unmedicated children and adolescents diagnosed with OCD before and after CBT. The brain activity of children and adolescents diagnosed with OCD will be compared to age-matched healthy controls during performance of the simon task and our virtual reality (VR)-based assessment of multiple learning and memory systems. In addition, functional connectivity within frontostriatal circuits in children and adolescents with OCD will be compared to age-matched healthy control children and adolescents. Anatomical and DTI data will also be collected so that we can begin to identify any structural and organizational abnormalities in these neural systems in children and adolescents with OCD compared to healthy control participants. Finally, children and adolescents with OCD will be offered a standard course of evidence based cognitive behavioral therapy (CBT) before rescanning (along with age-and gender-matched control participants) so we can explore changes in these circuits following treatment and the improvement of OCD symptoms. We will test the following hypotheses:

1. Compared to healthy controls, children and adolescents with OCD will have increased activation in subcortical structures (insula, and putamen) comprising a right hemisphere dorsal frontostriatal circuit while performing a self-regulatory control task (Simon task).
2. Compared to healthy controls, children and adolescents with OCD will have increased activation in the dorsal striatum associated with the receipt of rewards during the habit learning task and decreased activation

in ventral frontostriatal and mesolimbic areas (amygdala and hippocampus) associated with reward receipt during the reward-based spatial learning task.
3. Compared to healthy controls, children and adolescents with OCD will have increased connectivity within task-related dorsal frontostriatal circuits and decreased connectivity within ventral frontostriatal circuits during performance of the Simon and reward-based spatial learning tasks, respectively.
4. Activation within dorsal frontostriatal circuits will correlate positively and activation within ventral frontostriatal circuits will correlate inversely with symptom severity in the OCD children and adolescents, suggesting that these circuits are functionally more impaired in those with more severe symptoms.
5. Compared to healthy controls, children and adolescents with OCD will have increased fractional anisotropy (FA) within dorsal frontostriatal circuits and decreased FA within ventral frontostriatal circuits.

Exploratory Hypotheses:
We will explore change in these circuits in children and adolescents with OCD following CBT compared to non-specific changes in the control group. We hypothesize that (1) group differences in the patterns of brain activations and connectivity will decrease from baseline. (2) In the children and adolescents with OCD who meet the definition of responder status (clinical global impression scale of improvement equaled to 1 or 2), we hypothesize that change in the function and connectivity within these circuits will be associated with change in OCD symptoms.

Group differences in cortical thickness and subcortical volumes before and after CBT will also be explored.

Description of Subject Population

Sample #1

Specify subject population
Children/Adolescents diagnosed with OCD
Number of completers required to accomplish study aims
40
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
5-17

Sample #2

Specify subject population
Healthy Controls
Number of completers required to accomplish study aims
40
Projected number of subjects who will be enrolled to obtain required number of completers
40

Age range of subject population
5-17

Gender, Racial and Ethnic Breakdown

We will recruit all ethnic and racial categories. We plan to recruit a sample that is at least as ethnically and racially diverse as the population of the United States. According 2010 U.S. Census, there were 16.3% Hispanic and 83.7% non-Hispanic; racially, there are 72.4% White, 12.6% Black, 4.8% Asian, and 10.2% Other. Based on our experience and the demographics served by our institution, we expect the subject racial distribution to be approximately 73% White, 18% Black, 9% Asian, and for the ethnic distribution to be approximately 22% Hispanic. OCD is believed to occur more frequently in males. Thus, this study population will contain a ratio of boys to girls of roughly 3:1.

Because of our location in New York City and our history recruiting for studies like these, we do not anticipate problems recruiting ethnic or racial minorities. The final ethnic and racial composition of our sample will depend not only on who we screen, but also who is eligible and agrees to participate in the study.

To encourage minority participation, we will promote awareness of our research project among minority individuals in order to ensure the continued diversity of our sample. These efforts will include: 1) placing advertisements in media outlets popular with minority groups; 2) contacting local minority organizations and clergy to provide information about our research program; and 3) involving minority research staff in patient recruitment. These efforts are facilitated by the location of our institution in one of the most ethnically diverse neighborhoods in New York City (Washington Heights) and by the cultural diversity of the staff of the Children's Day Unit (e.g., bilingual staff of Hispanic background).

Description of subject population

We plan to recruit approximately 80 individuals ages 5-17 in this study. Participants will have a current diagnosis of OCD or no psychiatric diagnosis (healthy control).

Recruitment Procedures

Describe settings where recruitment will occur

The study will recruit pediatric participants diagnosed with OCD from the CAPES Evaluation Service and the Pediatric Anxiety and Mood and Research Clinic (PAMRC), which is part of the Children's Day Unit, and is directed by Drs. Rynn and Goldberg. The CAPES/PAMRC provides free expert consultation, evaluation, and treatment referrals for children and adolescents suffering from mood and anxiety disorders. OCD self-help organizations such as the International OCD Foundation will be contacted to further publicize the existence of this study.

Participants and their parent/caregiver will be assessed with an IRB approved phone screen (see attached

phone screen). We do not communicate to families that we will destroy their screening information if they do not come in for a study visit. Regardless of study participation, we enter the information from the phone screens into a deindentifed and password protected database.

Morgan Stanley Children's Hospital (CHONY)
Children and adolescents diagnosed with OCD will also be recruited through the patient resources and clinics at the Morgan Stanley Children's Hospital of New York-Presbyterian. After a parent/guardian gives permission to the clinic staff to refer a child/adolescent patient to the study, we will follow the screening procedures detailed in the study procedures section. We would also like to send a recruitment letter and/or pamphlet to all the parents/guardians with children/adolescents who are being treated in these outpatient clinics letting them know about our research. We will give this letter and/or pamphlet to the clinicians at each clinic and they will distribute the letter to the parents/guardians of their patients. Please see the attached recruitment letter and brochure we would like to distribute.

Columbia University Center for Anxiety and Related Disorders (CUCARD) (Director: Anne Marie Albano, PhD)
Children and adolescents with OCD will be recruited through the CUCARD. Dr. Albano collaborates with Dr. Rynn on other treatment research projects in the area of pediatric anxiety disorders. The CUCARD sees 300 new children and adolescents per year referred for anxiety disorders, and each child/adolescent and family are approached for participation in research projects. Recruitment procedures from this clinic will be the same as those above (CHONY).

Advocacy and Support Groups
OCD participants will also be recruited through scientific presentations to patient advocacy and support groups, such as the OCF (Obsessive Compulsive Foundation). We will also set up advertisements in their newsletters and on their internet websites and distribute recruitment letters.

Craigslist
Participants with and without OCD will be recruited through the volunteers section of the Craigslist website. We will post advertisements on the website biweekly with a brief description of the study (see attached craigslist postings). We will also post this description on other websites and pages relevant to OCD and anxiety disorders, consistent with the recruitment methods in IRB #6574.

Facebook and Twitter
Participants will be recruited via Facebook (www.facebook.com). We will post a description of this study on a page created for Dr. Marsh's Cognitive Development and Neuroimaging Lab and the facebook page for the Columbia Pediatric Anxiety and Mood Research Clinic, as well as on other pages relevant to OCD and anxiety disorders. The description of our study posted on these Facebook pages will inform treatment providers, support group leaders, parents and guardians of the research being conducted under this protocol. Facebook will not be utilized to inform children/adolescents of our studies. Facebook will not be used to contact children/adolescents. Despite precautionary measures enacted to deter children from responding to our postings, if a child/adolescent does respond to a Facebook posting, he/she will be asked to speak with her/her parent or guardian regarding he/her interest in participation in the study who then may contact us. The same IRB approved description of our study and a list of tweets (see attached list of tweets) will be posted on our lab twitter page on twitter.com.

Linkedin
We will use Linkedin to communicate with colleagues about our research efforts. A web announcement will be sent including our lab website, Facebook, and Twitter page links for their reference and for referring potential participants. As with Facebook and Twitter, if a child/adolescents contacts us directly after being referred by one of our colleagues, he/she will be asked to speak with a parent or guardian regarding interest in participation in the study.

RecruitMe: Columbia
Participants with OCD and healthy controls will be recruited through Columbia University's Recruit Me, an online tool to connect potential research participants with researchers conducting relevant studies.

Flyers
Participants diagnosed with OCD and healthy controls will also be recruited through flyers posted in the community. We will post flyers on bulletin boards in Columbia University Medical Center buildings as well as in local laundromats, grocery stores, public libraries, and community centers. Please see the attached flyers.

Private Practice
Participants diagnosed with OCD will be recruited through colleagues who see patients in private practice. Recruiting patients seen in private practice will enable us to gain a more diverse demographic and socioeconomic sample than would be found in the Washington Heights area alone. We will provide clinicians with a list of target diagnoses and a brief description of the purpose and procedures of our protocol, as well as letters for families who express interest in our research. The clinicians will initially approach parents or guardians to ascertain their interest in our protocol. Parents/guardians that express interest in our MRI study and want to hear more about it will be asked for permission for a member of our research team to contact them. With this verbal permission, members of our research team will follow up with a telephone call to read through a recruitment script detailing what we want to do and what would be expected of their child, and to administer screening procedures (please see recruitment script and screening questionnaire).

Healthy Control Recruitment
In addition to advertisements on Craigslist and flyers in the community, normal controls will be recruited from community-based telemarketing lists of households characterized by zip code, age, gender, ethnicity, and income level (Info USA based in Omaha, Nebraska. Phone #: 1-888-289-5478).

Healthy Control Recruitment Procedures: Introductory letters will be sent by the research team to randomly selected households containing potential participants with a demographic profile matching the clinical sample. We will also contact by telephone the parents of the families first contacted by letter. We will explain the purpose and design of our study, encouraging parents to ask questions about the project (see attached Telephone Recruiting Script). Parents of children who are interested in participating will then be screened for eligibility (see attached Telephone Screening Questionnaire). If their child meets inclusion criteria for the study, they will be approached for enrollment in the study.
How and by whom will subjects be approached and/or recruited?

Research staff from Dr. Marsh's Cognitive Development and Neuroimaging Lab and the PAMRC team may approach and discuss the research study with potential participants who have given permission to be contacted about research. Research staff will be responsible for fully explaining the details of the study, answering any questions, and consenting the participants if they are interested in the study.

How will the study be advertised/publicized?

IRB-approved radio/newspaper/web advertisements and flyers will be used to recruit participants.

The study will be publicized in the following ways:
1. Delivery of letters and pamphlets to patients by clinicians and researchers who practice at one of the recruitment sites listed above
2. Advertisements on patient advocacy and support group websites, listservs, and newsletters, as well as through scientific presentations to these groups
3. Research study announcements on Craigslist.com and Facebook.com, RecruitMe: Columbia
4. Mailings to households from community-based telemarketing lists
5. Flyers posted in the community
6. Pamphlets sent to individuals interested in referring individuals from one of the recruitment sites listed above

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
NCT02421315

Concurrent Research Studies

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

Participants in this study may be recruited and may be screened using the phone screens from the following studies:

- NYSPI IRB #6019R entitled, "Evaluation at the NYSPI Child Psychiatry Research Clinic."
- NYSPI IRB #6574 entitled, "Novel Medication Strategies Targeting Brain Mechanisms in Pediatric OCD."
- NYSPI IRB#6345R entitled, "Biobehavioral Assessment of Stress in Adolescent Pregnancy: Perinatal Outcomes
- NYSPI IRB# 6450 entitled, "The Effects of Prenatal Stress and Poor Nutrition on Brain and Cognition"

Inclusion/Exclusion Criteria

Name the subject group/sub sample
OCD patient group
Create or insert table to describe the inclusion criteria and methods to ascertain them

CRITERION	METHODS OF ASCERTAINMENT
1. Participants must be 5-17 at the time of consent	• Telephone Screening Questionnaire • Inquiry at time of consent by trained research staff
2. DSM-IV Diagnosis of OCD as the principal problem	• IE will administer the Anxiety Disorders Interview Schedule (ADIS). The ADIS will be used as a diagnosis measure • Study MD will conduct a clinical exam to confirm diagnosis • CYBOCS scores ≥ 16 • In addition previous clinicians will be contacted to discuss diagnosis
3. Not on psychotropic medication and not receiving current psychotherapy for OCD	• Telephone Screening Questionnaire • Clinical interview • medical records obtained by research team • In addition previous clinicians will be contacted to confirm treatment-naivety or psychotropic medication free for at least 3 months
4. Written informed assent by the participants (8 and older) and consent by the parent	• Consent interview by trained research staff (see consent procedures).
5. Participants and a parent/guardian must be able to read and understand English	• Telephone screening questionnaire • Inquiry at time of consent by trained research staff

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

CRITERION	METHODS OF ASCERTAINMENT
1. DSM-IV current diagnosis of major depressive disorder, attention-deficit hyperactivity disorder, Tourette's/Tic Disorder, or substance/alcohol abuse	• Telephone Screening Questionnaire • Clinical Interview
2. DSM-IV lifetime diagnosis of psychotic disorder, bipolar disorder, eating disorder, pervasive developmental disorder, or substance/alcohol abuse	• Telephone Screening Questionnaire • Clinical Interview
3. Active suicidal ideation	• Telephone Screening Questionnaire • Clinical Interview
4. Females who are pregnant or nursing	• Telephone Screening Questionnaire • Urine pregnancy test
5. Major medical or neurological problems	• Telephone Screening Questionnaire • Medical history obtained by study psychiatrist
6. Presence of metallic device or dental braces	• Telephone Screening Questionnaire • New York Psychiatric Metal Screening Questionnaire
7. IQ<80	• All participants will be administered the Weschsler Abbreviated Scale of Intelligence II (WASI-II) to confirm IQ
8. A current or past diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS)	• Telephone Screening Questionnaire • Clinical Interview

9. Individuals who are currently receiving CBT, other forms of psychotherapy, or psychotropic medications	• Telephone Screening Questionnaire • Inquiry at time of consent by trained research staff • Medical history obtained by study doctor
10. Individuals who have received a full course of CBT in the past	• Telephone Screening Questionnaire • Inquiry at time of consent by trained research staff • Medical history obtained by study doctor
11. A positive pregnancy test	• Based on pregnancy test given to all post-menarchal females onsite prior to the MRI scan
12. Positive urine screen for illicit drugs	• Based on urine toxicology assessment for participants 12 and up
13. Inability of participant or parent/guardian to read or understand English	• Telephone screening questionnaire • Inquiry at time of consent by trained research staff member

Inclusion/Exclusion Criteria #2

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

CRITERION	METHOD OF ASCERTAINMENT
1. Participants must be 5-17 at the time of consent	• Telephone Screening Questionnaire • Inquiry at time of consent

	by trained research staff
2. Written informed assent by the participants (8 and older) and consent by the parent	• Consent interview by trained research staff (see consent procedures)
3. Participants and a parent/guardian must be able to read and understand English	• Telephone Screening Questionnaire • Inquiry at time of consent by trained research staff

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

CRITERION	METHOD OF ASCERTAINMENT
1. Any current or lifetime psychiatric diagnosis	• Telephone Screening Questionnaire • Clinical Interview
2. Active suicidal ideation	• Telephone Screening Questionnaire • Clinical Interview
3. Females who are pregnant or nursing	• Telephone Screening Questionnaire • Urine pregnancy test
4.Major medical or neurological problems	• Telephone Screening Questionnaire • Medical history obtained by study psychiatrist
5. Presence of metallic device or dental braces	• Telephone Screening Questionnaire • New York Psychiatric Metal Screening Questionnaire
5. IQ <80	• All participants will be administered theWechsler Abbreviated Scale of Intelligence II (WASI-II) to

	confirm IQ
6. A current or past diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS)	• Telephone Screening Questionnaire • Clinical Interview
7. A positive pregnancy test	• Based on pregnancy test given to post-menarchal females onsite prior to MRI scan
8. Positive urine screen for illicit drugs	• Based on urine toxicology assessment for participants 12 and older
9. Inability of participant or parent/guardian to read or understand English	• Telephone screening questionnaire • Inquiry at time of consent by trained research staff

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

Prior to initiating screening procedures, research staff will obtain assent from the child and adolescent participants and consent from their parent/legal guardian by describing the purpose and nature of the research study and answering any questions from the families. The participant's parent/legal guardian will receive copies of the signed consent/assent forms.

Describe Study Consent Procedures

Each member of the research team has been extensively trained in consent procedures by Drs. Rynn and Marsh and has completed the NYSPI CITI training modules. The person obtaining consent will explain the protocol and associated risks to the prospective participant's parent/guardian. They will review the study objectives and procedures with the parent/guardian and ask him/her to read the attached consent form. The research team will also answer any questions the parent/guardian may have and ensure that the participant's parent/guardian understands that information collected as part of this study may be used in the future to answer other research questions not specified in this protocol as we learn more about the diagnoses and neurobiological mechanisms of interest. Once the research team member obtaining consent feels confident the participant is comfortable with the requirements of the study, they will obtain informed consent from the parent/guardian by having him/her sign the consent form. The consent process will be conducted after the telephone screening but before any other part of the study is conducted.

Because we will collect medical histories from all participants, each participant's parent/guardian will be asked to sign a HIPPA form prior to review of his or her child's medical history and prior to participation in the study. Permission to review medical histories is thus documented in writing. This form is designed to inform parents/guardians of their child's rights to privacy and of measures that we will take to keep their information as secure as possible according to the law. Our HIPAA form is in accordance with all federal and state regulations as laid out by the Office for Human Research Protections.

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

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
A waiver of consent is needed in order to obtain verbal consent from potential participants during the study phone screen. Please refer to 45CFR46.116(d) for justification of this waiver.
Explain why your research can not be practicably carried out without the waiver or alteration
As it is not practical to get written consent prior to conducting the phone screen, we instead get verbal consent from participants and/or their parents at the beginning of each phone screen. The staff member conducting the phone call documents that verbal consent was obtained.
Describe whether and how subjects will be provided with additional pertinent information after participation
N/A

Assent Procedures

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

The trained member of the research team who obtains assent will explain the protocol and associated risks in language that is appropriate to the prospective participant's developmental level. Assent will only be obtained from children 8 years and older. The trained member of the research team will review the study objectives and procedures with the participant and ask him/her to read the attached assent form. The research assistant will also answer any questions the participant may have. Once they feel confident the participant is comfortable with the requirements of the study, they will obtain parental permission as well as assent from the participant by having him/her sign the assent form. The permission and assent process will be conducted after the telephone screening but before any other part of the study is conducted. All efforts will be made to coordinate procedures (neuropsychological assessment, parent/participant interviews, and MRI) into a single day; however, the child/adolescent will be given the option of a second day for the MRI if he/she is fatigued or has a preference. If the participant (or parent/guardian) chooses to divide the study into two days, the participant will be verbally reminded of the key points of the assent form and procedures of the study on the second day.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Gindea, Sophie
Hill, Kelsey
Stefan, Mihaela
Steinberg, Emily
Wei, Chiaying
Yanes-Lukin, Paula, PHD
Type in the name(s) not found in the above list

Goldberg, Pablo, MD
Marsh, Rachel, PhD

Study Procedures

Describe the procedures required for this study

Columbia University Pediatric Anxiety and Mood Research Clinic (CU-PAMRC)
The study will be conducted at the Columbia University Pediatric Anxiety and Mood Research Clinic (PAMRC). PAMRC is an outpatient clinic and a research day treatment program (CDU) that provides services for the psychiatric and educational need of children and adolescents participating in research

protocols at NYSPI. Most of the children have either failed or not completely responded to first line treatments for mood, OCD, or other anxiety disorders. School services are provided by PS186X, a New York City public school located on the unit during the academic year starting from September through June. In addition, during the 6 week summer program in July and August, the PAMRC provides educational tutoring. This unit provides continued clinical care for children and adolescents after their participation in an IRB approved protocol at no cost. Led by Drs. Rynn and Goldberg, the staff consists of a research medical director, Dr. Pablo Goldberg, a research nurse, a social worker, psychologists, and trainees. Although this protocol is an outpatient protocol, if an adolescent requires additional support or requires a higher level of care, the adolescent may be admitted to the PAMRC partial program that runs Monday through Friday from 8:30AM to 3:30PM where the adolescent can be closely monitored, receive educational credit, and additional supportive service. For children under the age of 12, the PAMRC team is available for the child and parent to come in for daily check-in visits for support and monitoring, but it does not have educational programming for children under 12.

Screening

Upon consenting, participants will complete all screening procedures. Those participants who turn 18 after assenting while still enrolled in the study will be re-consented as adults. Study staff will confirm and document that they agree to their parents' continued involvement in the study. Screening visits will be coordinated to be completed in 1 day, but may be spread out over the course of 2 days to allow sufficient time to obtain thorough medical and psychiatric history to ensure the patient's safety and eligibility/ineligibility in the study.

- **Diagnostic Assessments:** Anxiety Disorders Interview Schedule- Child/Parent version (The child version will be administered to all participants. The parent version will be administered to parents of all participants); Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS), OCD onset form; Clinical Global Inventory- Severity Scale; Family History Screen and Isolated Tics/Tic Disorder Assessment Questions; Hamilton Depression Scale (HAM-D)
- **Feasibility and safety measures:** Columbia Suicide-Severity Rating Scale
- **Medical:** Tanner Scale, vital signs, height and weight measurements to ensure participant safety prior to the MRI scan, pregnancy test and urine toxicology
- **MRI:** MRI Screening Questionnaire (The screening questionnaire includes questions regarding inclusion/exclusion criteria, including the presence of ferromagnetic implants, pubertal status, and pregnancy)

Any adverse events that occur during screening and/or any information that warrants clinical attention (i.e. suicidal ideation, intent to harm oneself/others) will be reported immediately to Drs. Rynn and Marsh, and proper interventions and referrals will be made.

Our teams believe research participation in the study would be enhanced by adding an educational opportunity/lesson to the screening or baseline healthy control study visits . During either of these visits, a research staff member, under Dr. Marsh's supervision, will educate the participant and their parent/guardian about MRI and the application of MRI to the study of brain development and psychiatric illnesses.

Baseline Study Visit

After completing the screening procedures, eligible participants will proceed to the baseline study visit. We will make every effort to schedule study procedures so that they do not interfere with the school day, especially for the control group. Should a family of a child/adolescent with OCD in search of treatment decide to participate in an in-person screen during a school day (times), we will leave that decision up to the family. The baseline study visit will include optional training in the Mock scanner, pregnancy testing, an MRI scan, Neuropsychological testing and completion of self-report forms. These procedures are described below:

Mock Scanner or MRI Simulator : The participant will have the option to undergo training for the MRI scan in an MRI simulator. Two software programs are used in the MRI simulator: SimFx and Motrack. SimFx software simulates the ambient scanner sound and the active scanning noise. Motrack software uses trackSTAR to monitor how much a participant moves, through the use of a sensor attached to the participant's head. The purpose of the MRI simulator is to provide a realistic scanning experience to help the participant gradually acclimate to scanning procedures**.**

Pregnancy Test: All females who are post-menarchal will be required to take a pregnancy test prior to the MRI scan. In addition, all post-menarchal females will be required to take a pregnancy test at the screening visit to ensure eligibility. The tests will be conducted on-site after the signing of the consent/assent forms and will be paid for by the study. Urine samples will be collected and pregnancy tests done on the day of the screen and MRI scan. Children and their parents will be told about the results of pregnancy tests done on minors. The participant must have a negative pregnancy test in order to participate in this study. The trained clinician (i.e., professionally trained, bachelor's or higher level clinician) will conduct the pregnancy test and discuss the results with the parent and child. 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 Drs. Rynn and Marsh and other senior staff based on all available data on the family. In the rare instance of a positive pregnancy test, a trained clinician will provide appropriate information and referrals. The participant will be encouraged to consult with heir primary physician or with a family planning clinic.

MRI Scan

Pulse Sequence	Approximate Scan Time
fMRI	50 minutes
Anatomical	25 minutes
DTI	10 minutes

*** see attached for full pulse sequence**

For the MRI procedures, the participant will be instructed to lie as still as possible within the magnet for 90 minutes. All precautions and protections will be given to the participant to ensure that they are as safe and comfortable as possible. For the participant’s comfort within the scanner, they will lie on a padded table with a pillow on which to rest their heads. A blanket will also be provided to keep participants warm during the procedure. If the participant appears nervous or anxious, a trained member of the research staff will remain with them inside the scanning suite for the duration of the scan. The participant will be given a squeeze ball to terminate the scan at any time. If they squeeze the ball, they will be removed from the scanner immediately. All of the MRI procedures will be conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. Conducting these procedures will be an accredited Magnetic Resonance

Technologist (B.M.R.) and two members of the research staff (Bachelor's Level or Higher) trained in the acquisition of MR images by Dr. Marsh, as well as in procedures for testing human participants.

Functional MRI procedures will include the completion of the Simon Spatial Compatibility Task (Simon) and the Virtual Reality Maze Tasks (VR). EyeLink 1000 Plus system will be used during these tasks to observe and analyze the participant's eye movements during each task. By following the participant's gaze we will be able to determine whether or not the participant is focused on the stimulus presented on the screen.

The fMRI tasks are as follows:
1. In the Simon Task, participants are instructed to respond with a button press each time an arrow is displayed to indicate the direction in which it was pointing. Most of the stimuli will be arrows that were displayed on congruent sides of the screen (e.g. left-pointing arrows displayed on the left side of the screen). Only a few of the stimuli will be presented on the incongruent side of the screen (e.g. left-pointing arrow displayed on the right side of the screen). Participants will be asked to inhibit the response to the location of arrow display and indicate their response to the direction of the arrow displayed.
2. The VR task is designed to study declarative and procedural/habit-learning and memory systems. Participants will be told that they will find themselves in the center of a virtual maze with 8 arms extending outward and that their task is to find hidden rewards ($ signs). The task will use a joystick to navigate through the environment. There will be both a spatial (declarative) and an S-R (procedural) learning condition. In the declarative version, participants must remember the locations of extra-maze cues (e.g. mountains, trees, and a sunset) to find the rewards. In the S-R version, participants must learn to approach lit arms to obtain rewards. Here, the extra-maze cues will be randomly interchanged at the end of each trial, thus destroying any possibility of using spatial learning to find the rewards.

In total, we will collect data from three modalities of MRI within this study: functional MRI; anatomical MRI; and diffusion tensor imaging (DTI). Between the functional and structural (anatomical and DTI) scans there will be a break for participants to stretch and use the bathroom. Child participants will be given the option to watch a segment of a child-friendly movie during the structural portion of the scan. Although our MRI Scans are for research purposes, T-1 weighted FSPGR anatomical images will be sent to a radiologist to be examined for evidence of mass effects or hydrocephalus within 1 month, and any significant abnormalities will be shared with parent of a child participant. One radiological report will be acquired after the baseline scan because the follow-up scan will take place within 16-20 weeks of the first scan. When necessary, referrals will be made for clinical scans. We receive written reports once a month from the radiologist documenting his findings from all readable scans, and any reports that suggest the need for follow up will be addressed by Drs. Rynn and Marsh immediately. In the rare case of obvious, serious lesions or tumors that need to be immediately followed up clinically, the radiologist will contact Dr. Marsh at the time the reading is completed.

MRS Data Acquisition

All MRS data will be acquired on our NYSPI scanner with a standard quadrature single-channel head coil in a total examination time of approximately 60 min, including scan setup. First, a standard T1-weighted volumetric MRI series will be acquired for use in estimating the proportions of gray matter, white matter and CSF content of the head of the caudate through tissue segmentation. Second, glutamate (Glu) levels will

be recorded from the head of the caudate using MRS. The recorded 4D raw data set will be processed using standard procedures. The striatal voxels will be selected from the spectroscopic imaging grid after acquisition and post-processing, and then analyzed for Glu content using versatile software, XsOSNMR, developed in Dr. Shungu's laboratory at Weill Cornell (collaborator on PSF # 6574). The Glu data will be quantified as peak area ratios relative to the robust unsuppressed water resonance (W) in a spectroscopic imaging data set that will be acquired in just 4 min using the same spatial parameters as in the PRESS SI sequence.

Neuropsychological Assessments
All participants will undergo neuropsychological testing that includes measures of intelligence, impulse control and sustained attention, memory, and learning. These behavioral measures, conducted either before or after (but always within a week of) the scanning session for each participant, will be used in correlation analyses with our MRI measures of brain function, connectivity, and morphology.These measures will be used in correlation analyses with measures of regional brain activation. (Please see "Instruments" below for a complete listing of these measures).The tests assessments will all be administered at the New York State Psychiatric Institute by a trained member of the research staff (Bachelor's level or higher).

Self-reports
Participants and their parents will fill out self-report forms during the baseline study visit and during screening. Please see the section on assessment instruments for more detail about these self-reports.

Cognitive Behavioral (CBT) Treatment
Upon completion of the diagnostic interviews, neuropsychological tests, and baseline MRI scan, pediatric participants diagnosed with OCD will be offered standard evidence based CBT treatment in the PAMRC. The treatment team will offer a course of CBT (45 minute sessions for 12 to 16 weeks), augmented by medication treatment when clinically indicated based on the clinical treatment standards. This treatment will be overseen by Drs. Rynn, Goldberg, Yanes-Lukin and Puliafico. Cognitive-behavioral therapy (CBT) is a treatment based on learning and cognitive theories. CBT for OCD involves gradually exposing patients to anxiety provoking stimuli while having patients refrain from engaging in compulsive rituals and/or avoidance behaviors. There are three major components of CBT treatment for OCD, specifically: (1) exposure to anxiety provoking stimuli, (2) response prevention, and (3) cognitive techniques intended to decrease anxiety during the exposure and response prevention processes. CBT has demonstrated clinically significant effects in reducing pediatric OCD symptomatology in several randomized controlled clinical trials (Abramowitz, Whiteside, & Deacon, 2005, for review). We will use the following referral sources for those for whom treatment in PAMRC might not be suitable (CUCARD, CHONY, NYU Child Study Center, private practices etc.)

The study physician and psychologist will provide ongoing monitoring of treatment cases during the PAMRC weekly research meeting and at the midpoint CBT treatment (between 6 to 8 weeks) the study physician will be scheduled to clinically evaluate participants with the standard clinical PAMRC protocol. At this time, the study physician will administer the CSSRS and the CGI. He will also conduct a clinical review of symptoms. Additionally, the study therapist and/or independent evaluator will clinically evaluate the participant by administering the CYBOCS. If the study staff believe that the patient meets for clinical deterioration, following administration of these assessments, the physician will discuss with the family the option of augmenting treatment with medication. In addition to ongoing monitoring and treatment midpoint

physician evaluations, the study clinician will complete weekly clinical assessments, including the CGI, as indicated in the treatment manual "OCD in Children and Adolescents: A Cognitive-Behavioral Treatment Manual" by John March, M.D.

To ensure that EX/RP is delivered appropriately, treatment will be provided by clinicians trained in EX/RP and supervised by Anthony Puliafico, Ph.D. and Paula Yanes-Lukin, Ph.D., both of whom are experts in EX/RP treatment. To ensure fidelity, treatment for all participants will follow the treatment manual "OCD in Children and Adolescents: A Cognitive-Behavioral Treatment Manual" by John March, M.D. Clinicians will meet weekly with Dr. Puliafico or Dr. Yanes-Lukin for supervision on study treatment cases, and Drs. Puliafico and Yanes-Lukin will review treatment procedures to ensure fidelity and appropriate clinical care.

End of Study Visit

All treatment-seeking OCD participants will be asked to return for an end of study visit following completion of their treatment in the PAMRC. We will also ask age-and gender-matched control participants to return for an end of study visit, within 16 to 20 weeks of their first scan. Procedures for the end of study visit will be similar to those described for the baseline visit. The following assessments will be completed during the end of study visit:

Diagnostic and Safety assessments:

- **Diagnostic Assessments:** Anxiety Disorders Interview Schedule- Child/Parent version (Subsections of ADIS that were endorsed at baseline will be administered to all child/adolescent participants and their parents at follow-up.); Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS), Clinical Global Inventory- Severity Scale; Hamilton Anxiety and Depression Scale (HAM-D)
- **Feasibility and safety measures:** Columbia Suicide-Severity Rating Scale
- **Medical:** Tanner Scale, vital signs, and height and weight measurements to ensure participant safety prior to the MRI scan
- **MRI:** MRI Screening Questionnaire (The screening questionnaire includes questions regarding inclusion/exclusion criteria, including the presence of ferromagnetic implants, pubertal status, and pregnancy)

Self-Report Forms:

- Child Obsessive-Compulsive Impact Scale-Revised (COIS-R), Family Accommodation Scale (FAS), Sensitivity to Punishment and Sensitivity to Reward Questionnaire-Children (SPSRQ-C), Intolerance of Uncertainty Scale for Children (IUSC), Barratt Impulsivity Scale (BIS) Brief, **Media Use Questionnaire**

Neuropsychological Testing:

- Stroop Word-Color Interference, Continuous Performance Task, the Reinforcement Learning Go/no-go task, and the risk/ambiguity tasks

2nd MRI Scan:

- The MRI procedures and pulse sequences used in the second scan will be the same as those described for the baseline scan.
- The MRS data may also be collected from OCD participants who remain symptomatic at end of study. MRS procedures and pulse sequences used at end of study will be the same as those described for the baseline scan.

The purpose of the follow-up visit is to have information allowing us to compare brain structure and function before and after treatment in children and adolescents with OCD and to be able to examine the relationships with treatment response.

Follow-Up Care
Upon completion of CBT treatment, end of treatment assessments and MRI Scan, participants will be offered an additional 3 months of follow up care, consisting of 3 monthly booster sessions, and/or open medication management, if applicable. If a participant is withdrawn from the study or drops out of the study, he/she will also be offered 3 monthly booster sessions. In the event they prefer to be treated elsewhere, they will also be provided referrals to community providers. All participants will be assessed during these booster session OCD severity (using the CYBOCS and CGI-S by the IE). Patients and families will have the option of completing 1 m and 2m follow up assessments by phone and the 3m assessment will be conducted in person.

Clinical Deterioration
Any patient who is evaluated by the study clinician to have experienced worsening of CGI-S by two levels for two consecutive visits will be evaluated by the study physician to determine if medication augmentation is indicated and if other types of ancillary treatments are indicated (such as family therapy and education support). If the child/adolescent continues to show clinical deterioration during the study and further continuation under such circumstances would be detrimental to the child/adolescent, the participant will be withdrawn from the study. If the child/adolescent is withdrawn from the protocol, the child/adolescent will be eligible for 3 months of no cost treatment in the PAMRC, consisting of 3 monthly booster sessions.If the participant or the participant's parent/guardian would prefer outside referrals, arrangements will be made by the research staff.

Future Research
After finishing the study, we may contact healthy control participants about participation in future research studies such as ongoing or new research studies. Participants do not have to participate in future research and they can decline participation when contacted. Participants 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
Clinical Deterioration

Any patient who is evaluated by the study clinician **to have experienced worsening of CGI-S by two levels** for two consecutive visits will be evaluated by the study physician to determine if medication augmentation is indicated and if other types of ancillary treatments are indicated (such as family therapy and education support). If the child/adolescent continues to show clinical deterioration during the study and further continuation under such circumstances would be detrimental to the child/adolescent, the participant will be withdrawn from the study. If the child/adolescent is withdrawn from the protocol, the child/adolescent will be eligible for 3 months of no cost treatment in the PAMRC, consisting of 3 monthly booster sessions. If the participant or the participant's parent/guardian would prefer outside referrals, arrangements will be made by the research staff.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Diagnostic Assessments:
Anxiety Disorders Interview Schedule for Children for DSM-IV (ADIS-C/P Revised): This will be administered to the participant and parent/caretaker by the independent evaluator (IE) at screening to confirm the diagnosis of OCD and its age of onset.
Family History Screen (FHS): This screens for the presence of 15 psychiatric disorders among the participant's biological relatives. It is administered to a family informant (for those ages 6-17) or to the subject (ages 18-20), who reports on himself/herself and on other biological relatives. It will be administered by the MD at screening.
The Tanner Scale: This is a scale of physical development based on external primary and secondary sex characteristics. Participants look at pictures of pubertal stages and identify their pubertal stage.
Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS): The CYBOCS is a semi-structured measure of OCD severity with excellent inter-rater reliability, internal consistency, and test-retest reliability. It is validated in those starting at age 7 and used in studies up to age 20. The CYBOCS differs from the adult YBOCS only in its use of simpler language. The CYBOCS will be administered by IEs at screening or baseline and will be the primary outcome measure.
Hamilton Depression Scale (HAM-D, 17-item): This semi-structured interview which assesses the severity of depressive symptoms is validated for use in ages 7 and above. It will be administered by the IE at baseline.

Feasibility and Safety Assessments:
Columbia Suicide-Severity Rating Scale (C-SSRS): This is a semi-structured clinician rating of suicidal behavior, suicide attempts, and presence and intensity of suicidal ideation.
Client Satisfaction Questionnaire (CSQ): Used in prior studies, this scale includes questions about satisfaction with treatment (CSQ). It will be completed by the participant (and parent/caretaker for those < 18 and those 18-20 with permission). For children under the age of 12, the Research Assistant (RA) will be present in case of reading comprehension questions.

Self-Report Forms:

OCD onset Form- This is a questionnaire completed by parents and children, used previously in IRB # 6574, to gather information about the onset and severity of OCD symptoms. Following the completion of the questionnaire, the Independent Evaluator (IE) completes a composite form taking into account the parent and child reports.
Child Obsessive-Compulsive Impact Scale-Revised (COIS-R): This 27-item self-report questionnaire measures OCD-specific functional impairment. The COIS-R-C is a 3-factor structure youth-report form. The COIS-R-P is a 4-factor structure parent-report measure (completed by the parent/caretaker for those <18 and those 18-20 with permission). Both will be completed at baseline.

Family Accommodation Scale (FAS) (5 minutes): This scale consists of 12 items to assess the areas and the level of family accommodation to the patient's OCD symptoms. It will be completed by the parent at baseline.
Isolated Tics/Tic Disorder Assessment: The parent(s) of the participant will be asked five questions about family history of isolated tics and Tic Disorder. The questions were developed by investigator Blair Simpson and are administered as an addendum to the FHS.
Sensitivity to Punishment and Sensitivity to Reward Questionnaire-Children (SPSRQ-C): This questionnaire measures Gray's anxiety and impulsivity dimensions. The questionnaire will be used to assess reward sensitivity.
Intolerance of Uncertainty Scale for Children (IUSC): The IUSC is a 27-item, 5-point Likert-style rating scale of a child's negative reaction to uncertain or ambiguous situations on emotional, cognitive, or behavioral level. The rating scale is completed by parent and child. IUSC Child and Parent forms have been validated in samples of youth ages 7-17, and the outcomes of this psychometric study have been published in Psychological Assessment (Comer, Roy et al., 2009). Specifically, both the parent and child forms of the IUSC have demonstrated strong internal consistency, as well as convergent validity as evidenced by significant associations with anxiety, worry, and reassurance-seeking. Children with anxiety disorders score higher than matched non-referred community youth on both the parent and child forms. Moreover, receiver operating characteristic (ROC) analyses demonstrate acceptable overall utility for the measure in distinguishing youth with anxiety disorders from youth without anxiety disorders. In all, findings from this psychometric work provide support for the use of the IUSC for continuous measurement of children's ability to tolerate uncertainty.
Barratt Impulsivity Scale (BIS) Brief: The BIS Brief is an 8-item, 4-point Likert-style rating scale, adapted from the BIS-11 self report, and designed to assess the personality/behavioral construct of impulsiveness.
The Short Grit Scale: The Short Grit Scale is an 8-item self-report survey that measures persistence and commitment to long-term goals. It takes fewer than 10 minutes to complete and score, and is designed to be appropriate for children. The child reads or hears sentences like "I am a hard worker" and then chooses a response on a scale of 1 to 5 that best describes himself or herself.
Media Use Questionnaire: This questionnaire is a 5-item self-report survey that measures media use in youth (i.e. time spent on TV, video games, phone; types of video games, etc.) which was adapted from the Media Use measure in the PhenX Toolkit (#750700). It will be completed by the parent and child during the baseline visit.

Neuropsychological Testing:
Wechsler Abbreviated Scale of Intelligence (WASI-II): This estimates Full Scale IQ with excellent reliability and validity for ages 6-90. It consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The full assessment will be administered by an RA at baseline.

Stroop Word-Color Interference: This is a classic task of cognitive interference that is comprised of 3 subtasks. In task A (color naming), participants are asked to name as quickly as possible the color (red, green, or blue) of 126 dots, 5.6 mm in diameter, arrayed randomly in 9 columns and 14 rows on an 8.5 x 11 inch sheet of white paper, scanned left to right and then top to bottom. In B (word reading), they are asked to read as quickly as possible an equal number of similarly arrayed words ("red", "green", or "blue") printed in black ink. In C (color-word naming), they are asked to name as quickly as possible the ink color of a similar array of words written in incongruent colors. The time to completion of each task is recorded (A, B, and C, respectively). Stroop interference is calculated as C-[(AxB)/(A+C)].

The PhenX Toolkit Hand Dominance Measure: This measure assesses one's handedness, and is based off of the Edinburgh Handedness Inventory. The PhenX Toolkit is a collection of measures developed for researchers to use to combine or share data.

Continuous Performance Task: The Continuous Performance Task (CPT)is a standardize measure of sustained attention and impulsivity. Subjects are presented with a series of letters on a computer screen and are instructed to hit the spacebar on the keyboard whenever a letter is presented. However, subjects are instructed to not hit the spacebar when the letter "X" is shown.

Reinforcement Learning Go/no-go task:Participants will be presented with one of 5 images on each trial and must learn to press (i.e., 'Go') or not to press (i.e., 'NoGo') a button for each image. Two of the images are more associated with reward (i.e. participants gain points if they press the button upon presentation of those images); another two images are more associated with punishment (participants lose points if they press the button); and the last image is neutral. Not pressing the button is never associated with feedback and does not gain or lose points. By assessing whether subjects learn better to press or not to press the button (for the respective images), the task can determine if they learn better from rewards or punishments, respectively. The task consists of 150 trials: 3 blocks of 50 trials (each image presented 10 times with images randomly intermixed).

Stop Signal Task: Participants will perform a child-friendly visual stop-signal task, in which they will be asked to indicate the direction of an airplane with a button press. Eighty percent of the trials will be simple go trials. Unpredictability, on 20% of trials, a stop signal (cross) will appear with a delay after the airplane. Behavioral outcome measures will be the subject-specific stop-signal reaction time (speed of the stop process), the mean reactions time on the accurate go trials (speed of go process), and the error percentage on go trials (overall attention).

Decision-Making Tasks: These tasks investigate how individuals make decisions under risky or ambiguous conditions. Participants will make many choices between different amounts of money that they can receive at different times or with different likelihoods. The tasks will begin with a set of instructions and a couple of practice trials. Typically, two or more options will be presented simultaneously on the screen. For instance, one option might be a money amount to be received soon and the other might be another amount to be received later, or one option might be a money amount to be received with some stated or unstated likelihood and the other might be another amount to be received for sure. After a brief delay, the options will disappear and subjects will be prompted to state their choice by pressing a particular key on the computer keyboard. The trial will end with the subject's answer. The program will then move on to the next trial after a short delay. Each task will include 100-200 trials and will last approximately 15 minutes. Breaks will be provided and available anytime subjects require them. At the end, one of the participant's choices will be selected randomly to count for actual payment that will be given in cash ($0 to $66), immediately following their completion of the tasks. This payment mechanism ensures that the experiment is incentive compatible: participants don't know which choice will count for actual payment and will not be able to

change their selection during the payment phase, so the best strategy is to select the options they prefer most each time. Together these tasks will take approximately 30 minutes to complete.
The Weather Prediction Task: The Weather Prediction Task is a measure of probabilistic learning. The task is administered on a laptop computer (Dell). In the Weather Prediction task, subjects are required to "guess" whether card-like stimuli mean that the weather will be sunny or whether the cards mean that it will rain. On each of 50 trials, stimuli appear on the left side of the computer screen and subjects are prompted to press a key showing a sun or to press a key showing a rain cloud. Following correct responses, a happy face appears on the right side of the screen and children hear a high tone. Following incorrect responses, a sad face appears on the right side of the screen and subjects hear a low tone.

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
It is anticipated that the maximum time from the time of consent to completion of the first MRI scan will be no more than 4 weeks. For treatment-seeking OCD participants, this could delay their initiating treatment and thus cause them to have ongoing OCD symptoms. Dr. Rynn and her clinical team in the Children's Day Unit will be in contact with these participants and their families every week from the time of signing consent throughout the MRI scanning to evaluate their ability to continue in the protocol. All attempts will be made to schedule the scan within 2 weeks of consent, though we may require 4 weeks to accommodate participants' and their families' schedules. If clinically inappropriate to delay treatment, the case will be referred for treatment within our system or elsewhere. If a child suddenly met any exclusion criteria (e.g., active suicidal ideation) or no longer met the inclusion criteria of being "able to tolerate a treatment-free period," the patient would be removed from the study and referred for treatment. Patients may refuse to participate at any point and seek treatment.
Maximum duration of delay to standard care or treatment of known efficacy
same as above
Treatment to be provided at the end of the study
Following completion of treatment in the PAMRC (including 3 months of follow-up care following completion of study treatment) and all other study procedures, children with OCD will be referred to other clinical settings (outpatient mental health care clinics or private clinicians specializing in OCD) in the tri-state area if they need additional care.

Clinical Treatment Alternatives

Clinical treatment alternatives
Currently cognitive-behavioral treatment involving exposure and response prevention (CBT/ERP) and serotonin reuptake inhibitor (SRI) medication are considered the first line treatments for OCD. However, pharmacotherapies have relatively modest effects in OCD. CBT/ERP treatment is the mainstay of the treatment for OCD. Yet, CBT/ERP alone results in response rates of anywhere between 60% and 80%, and

fear of non-adherence to ERP is hypothesized to contribute to the lack of ERP efficacy across age groups.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Clinical and Neuropsychological Assessments: No risks are associated with these assessments. If the participant no longer wishes to continue the testing, they may stop at any time. All tests will be administered at the New York State Psychiatric Institute by a trained member of the research staff (Bachelor's level or higher). 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 reported immediately to Drs. Rynn and Marsh, and proper interventions and referrals will be made.

Diagnostic Interviews: No risks are associated with these diagnostic interviews. If the participant no longer wishes to continue the interview, they may stop at any time. All interviews will be conducted at the New York State Psychiatric Institute. The interviews will be performed by a trained member of the research staff (Bachelor's level or higher). 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 Drs. Rynn and Marsh, and proper interventions and referrals will be made.

Pregnancy Testing: No known risks are associated with pregnancy testing. If the results of the pregnancy test cause the participant and parent any distress, a trained member of the research staff will discuss the results with her, and appropriate referrals will be made.

Magnetic Resonance Imaging: Both the FDA and the NYSPI IRB have deemed MRI Scanning on the GE 3Tesla MRI Scanner at the New York State Psychiatric Institute to be classified as a non-significant risk.

CBT Treatment: There is a possibility that symptoms may not improve or could worsen during treatment. Any patient who is evaluated by the study clinician to be worse (CGI-S score of 5) for two consecutive visits will be evaluated by the study physician to determine if medication augmentation or other types of ancillary treatments are indicated (such as family therapy and education supporters). At this time, the study physician will discuss the possibility of withdrawing from the study or beginning medication treatment in conjunction with CBT.

In the case of combined treatment with medication treatment:
Adverse events will be closely monitored by the study physician and tracked using the CDU adverse event form. The study physician will review with the participant and their families the following potential serotonin reuptake inhibitor (SSRI) related adverse events: gastrointestinal complaints (nausea, pain, diarrhea, and constipation), dizziness, allergic reactions, increased anxiety or irritability, increased activation/restlessness, sleep changes (increased or decreased), sexual side effects, appetite changes (increase or decreased), unusual thoughts, sweating, fatigue, suicidal ideation/attempts/and or behaviors. In addition to these issues, the study physician will discuss with participants and their families the Food and Drug Administration advisory that the use of antidepressants like the SSRIs may lead to suicidal

thinking/attempts in depressed and anxious youth and that the FDA has placed product warning label with information highlighting the need for close observation for worsening of symptoms and the emergence of suicidality in children treated with these medications. This information will be a part of the consent process for the study so that families are aware of these issues when considering the addition of medication treatment. The study physician will review with the adolescents and their legal guardians, potential adverse events and to carefully monitor for any significant changes in mood, thinking, behaviors, and physical symptoms especially early in medication treatment. The adolescents and their families will be instructed to call the study physician with any concerns, and to call the 24 hour on call service at the Child/Adolescent Comprehensive Psychiatric Emergency Program (CPEP) for any emergency.

Describe procedures for minimizing risks
To reduce the potential for participant fatigue, we will offer several breaks to the participants throughout study procedures. Prior to the administration of the interviews, participants will be told that if any questions make him/her uncomfortable, he/she can ask to move on to the next question. This will be done to minimize any potential discomfort from the personal nature of the questions asked.

In EX/RP treatment, patients confront feared situations that are expected to produce moderate levels of distress initially. This initial fear reaction is essential to the treatment, as it allows the patient to habituate to situations in which he or she is excessively or irrationally fearful. Exposures to feared situations are carried out with the patient's advance knowledge and full consent. Such exposure procedures have produced considerable benefits in studies of children and adolescents with OCD. The only reported side effect has been transient increases in anxiety. These reactions will be closely monitored by study clinicians who have extensive expertise with pediatric OCD patients.

There is a possibility that symptoms may not improve or could worsen during treatment. Any patient who is evaluated by the study clinician to be worse (CGI-S score of 5) for two consecutive visits will be evaluated by the study physician to determine if medication augmentation or other types of ancillary treatments are indicated (such as family therapy and education supporters). At this time, the study physician will discuss the possibility of withdrawing from the study or beginning medication treatment in conjunction with CBT.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
In all records from this study, the names of participants and their family members will be available only to the team of researchers working on the study. Neither their names nor any identifying information will be used in any scientific reports from this study or from secondary data analyses conducted with de-identified data from this study. All the information obtained from the subjects is coded by number and kept in locked, confidential files. MRI data from this study will be stored on computers behind firewalls in our laboratory at NYSPI.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
The proposed analyses are unlikely to benefit any participant directly. The findings of this study, however, could increase understanding of brain structure and function, potentially, though indirectly, benefiting participants.

There may be benefits from the standard of care treatment received during the study. CBT/ERP is an evidenced-based treatment for adults and adolescents with OCD. Adolescents participating in the study will receive therapy from psychologists specifically trained in CBT/ERP therapy. The response rate of CBT/ERP could be up to 80%. Therefore, there is a good chance patients' symptoms will improve during the study.

Another direct benefit of study participation is that patients will receive a complete psychiatric and medical evaluation. During this evaluation, other potential problems may be identified by the interviews or questionnaires. In this instance, the study clinician will inform the participant that further evaluation and clinical assessment may be indicated, and will provide a brief summary of the information obtained to any treatment provider selected by the participant.

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.

Following completion of the MRI scan and MRI assessments (diagnostic interviews, clinical and neuropsychological assessments) healthy control participants, 11 years or younger, will be compensated $175 in the form of a gift card ($50 for the MRI scan, $50 for the neuropsychological testing, and $75 for the interviews), and OCD participants, 11 years or younger, will be compensated $100 in the form of a gift card ($50 for the MRI scan, $25 for the neuropsychological testing, and $25 for the interviews). Healthy control participants 12 years and older, will be compensated $175 for their time in the form of a check ($50 for the MRI scan, $50 for the neuropsychological testing, and $75 for the interviews). OCD participants 12 years and older, will be compensated $100 for their time in the form of a check ($50 for the MRI scan, $25 for the neuropsychological testing, and $25 for the interviews). Gift cards will be given to participants on site following completion of study procedures. For children 12 years and older, checks will be mailed to the participant's home address and can be expected to arrive within 2-3 weeks of the study visit.

In addition, participants will have the opportunity to earn $20 in the Virtual Reality (VR) fMRI task. Because these are measures of reward-based learning, participants must be rewarded immediately after the task has been completed based on their task performance so that we can accurately assess the functioning of reward circuits.

Participants will also be given the opportunity to earn up to $66 while playing computer tasks (risk/ambiguity tasks). Each participant can win $0-$66 on these tasks, combined. Participants will be rewarded with the amount they won immediately following the completion of these tasks.

Healthy control participants who return for a follow-up scan and assessments will again be compensated $175 for their time, and OCD participants who return will again be compensated $100 for their time (in the form of a gift card or check depending on their age) and given another opportunity to earn $20 in the VR task and up to $66 in the computer task. Compensation methods and procedures will be identical to those for the first MRI scan.

Additionally, families may receive up to $30 per visit to reimburse for transportation costs to and from the study site, as requested. This reimbursement will be offered in the form of a check mailed to the families' home address and can be expected to arrive within 2-3 weeks of the study visit.

References

References
N/A

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
fMRI OCD Brochure_7 6 17 BOLD.pdf
fMRI OCD Brochure_7 6 17 CLEAN.pdf
Upload copy(ies) of unbolded Assent Form(s)
Upload copy(ies) of bolded Assent Form(s)
Upload copy(ies) of the HIPAA form
HIPAA Child7006_for ACAR.pdf
Upload any additional documents that may be related to this study

TO PARTICIPATE

Your child may be eligible to participate in this study if he or she is:

- Diagnosed with obsessive-compulsive disorder
- 5-17 years old
- Not currently taking medication
- Not diagnosed with psychosis, a developmental disorder, tic disorder, or substance abuse
- Not in psychotherapy

Interested in learning more about our study?
Call us at 646-774-5793

We are happy to answer any questions you may have!

Kelsey Hill, B.A.
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NEW YORK STATE OF OPPORTUNITY. | New York State Psychiatric Institute

A CBT Treatment and MRI Research Study for Children and Adolescents with OCD (Ages 5-17)

The Cognitive Development and Neuroimaging Lab and The Columbia University Pediatric Anxiety and Mood Research Clinic

OCD Treatment and Research Program
1051 Riverside Drive
New York, NY 10032
http://www.columbiapsychiatry.org/pamrc

Columbia PAMRC

NYSPI IRB APPROVED #7006

What is Obsessive-Compulsive Disorder (OCD)?

We all have habits and routines; however, children and adolescents with OCD have habits and routines that **get in the way** of their daily lives. If your child's day-to-day life is affected by these symptoms, **OCD may be the cause.**

Symptoms of OCD

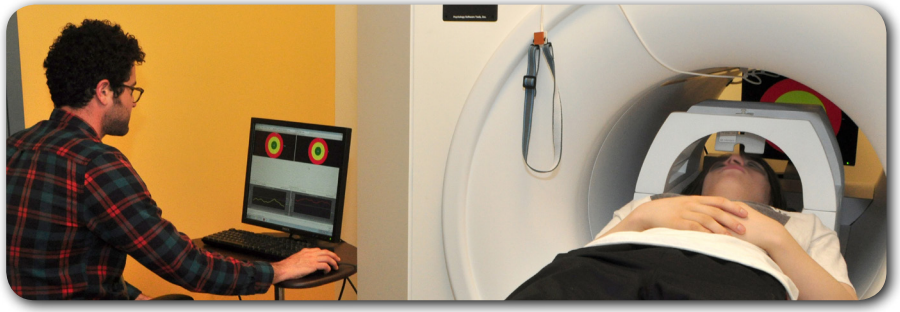
Obsessions	Compulsions
Repeated and unwanted ideas, impulses or thoughts that cause nervousness or fear	Performing repetitive behaviors to get rid of the uncomfortable fear or thoughts

What is Cognitive Behavioral Therapy (CBT)?

- **Cognitive behavioral therapy** is a type of therapy that focuses on changing thoughts and behaviors to help your child feel better.
- **Exposure and Response Prevention (ERP)** is a specialized type of cognitive behavioral treatment for OCD, where a therapist will help your child face their "scary" or "unpleasant" thoughts and **teach them skills** to be able to **resist OCD** compulsions.

What is an MRI?

- An **MRI** is a large tube shaped machine with a **magnet** inside that allows us to **take pictures of your brain.**
- Combining MRI scans from a large number of children allows us to learn more about **how brain areas are related to OCD**. This information can help us **improve treatments** for OCD.



What are the benefits of participating in this study?

- **Free** comprehensive diagnostic evaluation
- **Free** neuropsychological evaluation
- 12-16 sessions of OCD-specific CBT treatment by expert clinicians **at no cost**
- Additional **medication care** by study doctor specializing in OCD treatment, if needed
- **2 brain scans** in a Magnetic Resonance Imaging (MRI) machine before and after CBT treatment
- Up to **$240 as a "thank you"** for participating in this MRI research study

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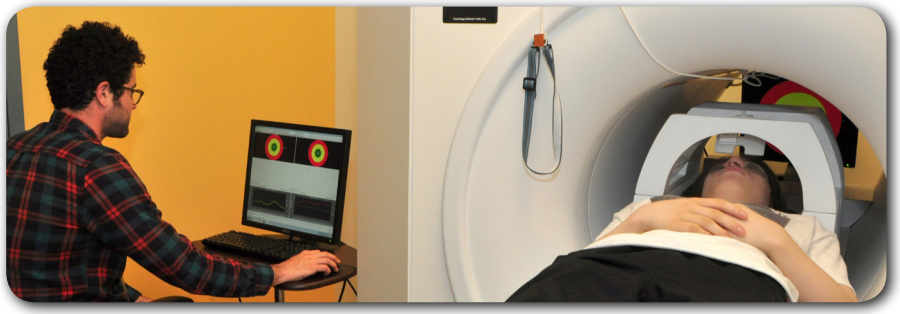

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New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study
(Child Version)

Protocol Number: 7006 **Principal Investigator:** Rachel Marsh Ph.D.

Name of Study: Overlapping Neural Circuits Implicated in Pediatric OCD

Before researchers can use or share any identifiable health information ("Health Information") about your child as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about your child as described below:

- New York State Psychiatric Institute (NYSPI), your child's doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form.

1. The Health Information that may be used and disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your child's clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be used and disclosed to:**
☑ Researchers and their staff at the following organizations involved with this Research:

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your child's health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your child's Health Information as described above, you understand that your child's Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your child's Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, your child may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, your child may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about your child as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Rachel Marsh, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, Unit 74 New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your child's clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your child's care, your child's Health Information will be given to you or your child's Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Parent/ Legal Representative Date

_____

Printed Name of Parent/Legal Representative

_____

Name of child

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**

STATISTICAL ANALYSIS PLAN

Functional MRI (fMRI) Data Processing
The Human Connectome Project (HCP) preprocessing pipelines[1] will be used to preprocess all multiband functional imaging data. Briefly, this will include gradient unwarping, motion correction, field map-based EPI distortion correction, brain-boundary-based registration of EPI to structural T1-weighted scan, non-linear (FNIRT) registration into MNI152 space, and grand-mean intensity normalization. The EPI data will be smoothed with a 4mm Gaussian kernel. Additional processing will be run in MATLAB (Mathworks, Natick, MA). Using commands from Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/) and FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) software, BOLD signal will be demeaned and detrended (AFNI 3dDetrend), despiked (AFNI 3dDespike -localedit), and bandpass filtered (FSL fslmaths 0.01-0.08 Hz). Nuisance regression of 24 motion parameters (bandpass filtered; 6 motion parameters, derivatives, and squares), as well as of average global signal from gray and white matter, and cerebrospinal fluid will be performed. Motion censoring[2] based on framewise displacement (FD; >0.2mm) and DVARS (z-score>3) will also be performed.

Structural MRI Data Processing
Two high-resolution T1-weighted BRAVO structural images will be averaged and bias field corrected. Data will then be processed in FreeSurfer[3,4]. This will include subcortical segmentation (left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens) and cortical parcellation (74 regions per hemisphere) based on the Destrieux atlas[5]. Output images will be visually inspected for quality.

Diffusion MRI Data Processing
Diffusion MRI data will be assessed for data quality and head motion. A structural connectivity matrix will be estimated for each participant using the standard MRtrix3 preprocessing pipeline[6], yielding a 164x164 symmetrical streamline count matrix for each participant using the FreeSurfer segmentations/parcellations noted above (148 cortical, 14 subcortical regions, and the left and right cerebellum). Using this approach, streamline count between brain regions is proportional to the cross-sectional area of white matter fibers connecting those regions. Thus, streamline count is a biologically plausible metric of "structural connectivity" proposed to represent the communication ‘bandwidth’ between regions, though it may indicate either sparse but fast (i.e. few large diameter axons) or dense but slow (i.e. many small diameter axons) connections[7]. Furthermore, streamline counts in macaques significantly correlate with connection strength from anatomical tract-tracing, supporting its validity as an indicator of fiber connection strength[8].

Hypothesis Testing:
Primary Outcome Analysis: Brain activation (i.e., BOLD signal) during performance of an fMRI task (Simon) that requires self-regulatory control in children and adolescent with OCD compared to age-matched healthy control (HC) participants.

First-level parametric analyses will be performed for each participant using the general linear model (GLM) provided by SPM12. For each participant, preprocessed time series data from all three Simon task runs will be modeled using a GLM with six conditions: 1) Incongruent correct trails preceded by congruent trials (cI), 2) Congruent correct trials preceded by incongruent trials (iC), 3) Incongruent correct trials preceded by incongruent trials (iI), 4) Congruent correct trials preceded by congruent trials (cC), 5) fixation trials, and 6) incorrect trials (incongruent or congruent), including trials with reaction times below the minimal RT of 200ms for stimulus detection and processing. These events will be convolved with the canonical HRF and then least-squares regression will be used to estimate parameters for each independent variable for each participant. Only correct trials will be included, given the limited number of incorrect trials. Runs in which a participant have more than 30% error rate on the task will be excluded from analyses. Because activation of task control regions is greatest when level of conflict is maximal (i.e., when incongruent stimuli are preceded by congruent stimuli)[9], analyses will focus on post-congruent trials. Parameter estimates averaged across the three runs will be used to produce a post-congruent Incongruent versus post-congruent Congruent (cI-cC) contrast for each participant to access brain activation associated with the engagement of self-regulatory control and resolution of maximal cognitive conflict.

Whole-brain second-level analyses of conflict-related BOLD signal will be performed using voxel-wise independent t-tests across groups (OCD vs. HC), adjusting for participants’ age, sex, and head motion (i.e., mean FD). A cluster-defining threshold (CDT) of $p<.001$ will be applied to all second-level group comparisons

maps, with Family Wise Error correction for multiple comparisons of $p<.05$ at the cluster level (FWEc). For each significant group difference detected, the direction of the effect will then be explored using within-group t-maps (CDT of $p<.001$, uncorrected). We hypothesize that compared to healthy controls, children and adolescents with OCD will have increased activation in subcortical structures (insula, and putamen) comprising a right hemisphere dorsal frontostriatal circuit while performing a self-regulatory control task (Simon task).

Secondary Outcome 1 Analysis: fMRI functional connectivity (FC) in task-control circuits in children and adolescent with OCD compared to age-matched HC participants. Whole-Brain Connectome-Level Analyses will be performed on the preprocessed fMRI data, computing FC-strength indices using Fisher Z-Transformation of the pairwise Pearson correlation coefficients between 352 regions (i.e., 333 cortical surface[10] and 19 subcortical[11] parcellated regions). Edge-wise functional connectivity analyses will then be conducted whole-brain across the resulting matrix comprised of 352 nodes and 123,904 edges. Analyses examining group differences will be adjusted for age at the time of scanning, sex, and head motion (mean FD) and conducted using the Network-Based Statistics (NBS) Toolbox[12] in MATLAB (Mathworks, Natick, MA). NBS controls for family-wise error rate using permutation testing to identify components or "clusters" of contiguous region-to-region connections. A statistical threshold of $p=.05$ with 20,000 permutations will be used. We hypothesize that youth with OCD will show altered functional connectivity between task-control circuit regions.

Secondary Outcome 2 Analysis: Regional subcortical volume and cortical thickness based on structural MRI data in children and adolescent with OCD compared to age-matched HC participants. Group differences in regional subcortical volume and cortical thickness will be assessed using linear regressions controlling for age and sex (ICV covaried subcortical volumes analyses). False discovery rate (FDR) will be used to correct for multiple comparisons (14 for subcortical analyses and 148 for cortical analyses). A follow-up vertex-wise analysis (QDEC in FreeSurfer) will probe group differences in cortical thickness (smoothed at 20mm), controlling for age and sex. Results will be corrected for multiple comparisons using Monte Carlo simulations with a vertex-wise threshold of $p<.001$ and an analysis-level threshold of $p<.05$ correcting for tests in each hemisphere (mri_glmfit-sim --cache 3 abs --2spaces). Given that prior meta- and mega-analyses of structural abnormalities in pediatric OCD by the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium ENIGMA OCD only showed small effect sizes in unmedicated youth with OCD compared to healthy participants[13], we do not expect significant group differences in subcortical volumes or cortical thickness.

Secondary Outcome 3 Analysis: Structural connectivity (streamline count) based on Diffusion Tensor Imaging (DTI) data in children and adolescent with OCD compared to age-matched HC participants. Structural connectivity matrices will be analyzed using the NBS toolbox[12] in MATLAB (Mathworks, Natick, MA). To avoid examining very sparse connections, those with median streamline count <100 will be zeroed out for exclusion from analysis. Group differences in structural connectivity (streamline count) will be tested using two one-tailed contrasts (OCD>healthy and healthy>OCD, controlling for age and sex, and corrected to an analysis-level $p<.025$ (10,000 permutations). We hypothesize that youth with OCD will show altered structural connectivity in the corpus callosum and in tracts integrating the fronto-partial and cingulo-opercular networks that are functionally altered in OCD.

Exploratory Analyses: In the children and adolescents with OCD, we will explore whether activation and functional connectivity is associated with OCD symptoms pre- to post-treatment with Cognitive Behavioral Therapy (CBT). These exploratory analyses will be restricted to regions/circuits in which group differences were detected (Primary Outcome and Secondary Outcome 1). Cross-lagged panel models will be constructed using IBM SPSS Amos to test for directional ("causal") relationships between OCD symptoms and fMRI measures pre- to post-CBT in the OCD patients. These models provide estimates of the extent to which a variable pre-CBT (e.g., connectivity) predicts another variable post-CBT (e.g., symptom severity), over and above the variability attributable to scores of that second variable (e.g., symptom severity) pre-CBT[14]. Thus, by controlling for the effects of each variable pre-CBT on the same variable post-CBT, pre-CBT variables then predict the residual, or change in that variable from pre- to post-CBT. the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)[15] total scores at each time point will be used as the OCD symptoms measure. The initial model will be adjusted for age, sex, and head motion (mean FD). All variables at each time point will be covaried to adjust for shared variance. Non-significant paths ($ps>.1$) will be removed one at a time within each model, and a chi-square difference test will examine whether each removal significantly reduced model fit. All stability paths will be retained, even if non-significant, to adjust for baseline levels of each variable.

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