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Research proposal

Brain plasticity underlying acquisition of new organizational skills in children

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Purpose of the Study and Background

Background

Organizational skill impairment occurs in many neurodevelopmental conditions, including attention-deficit/hyperactivity disorder (ADHD) [1] and contributes to school failure, a pernicious mediator of poor long-term outcomes.[2] Impairments in organizational skills have not been addressed by standard behavioral interventions, nor are standard medications for ADHD sufficiently effective for this specific functional domain.[3]

Organizational skills training (OST) was developed in response to the underperformance of stimulant medication to remediate organizational deficits and specifically to target the four impaired domains which worsen school performance, i.e., Tracking Assignments, Managing Materials, Time Management and Task Planning.[4] OST comprises in-person sessions with a therapist, during which previously learned skills are reviewed, new skills are taught and practiced, and instructions are given on when to use the new skill between sessions. Evidence from a two-site randomized controlled trial that OST can produce behavioral improvements in Children's Organizational Skills Scales (COSS) as rated by teachers, with large effect sizes which were maintained for up to 1 year[5] suggests that enduring changes in brain connectivity and intrinsic brain properties likely occurred.[6]

Purpose of the Study

We propose to identify functional changes in large-scale neural systems sub-serving response to intervention in elementary school-age children impaired in organizational skills. Specifically, we intend to use resting-state functional magnetic resonance imaging (R-fMRI) to capture the physiologic mechanisms underlying behavioral improvements following OST, i.e., the intrinsic functional connectivity (iFC) between dorsal anterior cingulate cortex (dACC) and anterior ventral striatum (aVS).

Study Design

This study includes two phases. The first phase (R61) was an open trial, single arm study, lasting 2 years, with completion of recruitment and data collection in July 2019. The second phase is a randomized two-arm (R33 phase) involving 1:1 randomization to waitlist (WL) control or to OST. In the R61 phase, we screened children (elementary school grades 3-5) to identify participants with organizational skill difficulties to undergo two magnetic resonance imaging (MRI) sessions: one within 2 weeks prior to OST treatment and one within 2 weeks of completion of the OST treatment.

The current randomized two-arm R33 phase will again involve the same treatment (OST) and pre- and post-treatment brain MRI scan. However, 50% of participants will be randomly assigned to receive OST within 2 weeks of successful completion of their first MRI scan (i.e., No-Wait study arm), while the other 50% will

be randomly assigned to receive OST after 12 weeks of waiting (i.e., Waitlist study arm).

Characteristics of the Research Population

Number of Subjects

In the R61 phase, we obtained complete datasets (i.e., high-quality pre- and post-OST scans and complete phenotypic data) from at least 22 participants. To reach this number, we enrolled over 50 children for in-person clinical/behavioral assessments, and scanning at least 30 eligible participants.

In the R33 phase, we anticipate screening 144 children to yield 86 with complete data from two sets of MRI scans, obtained after the same interval.

Only children are subjects in this study; parents (and if the child's teacher agrees, teachers) are informants who report on child's behavioral measures and are therefore not study subjects.

Gender of Subjects

We will recruit both males and females. Despite the marked male preponderance in neurodevelopmental disorders, we will endeavor to recruit at least 30% females.

Age of Subjects

This is a study of elementary school children in grades 3 – 5, who have one main teacher for at least three of the 4 core academic subjects (English Language & Arts; Math; History/Social Science; Science). The OST intervention is specifically designed for children in elementary school who have a single teacher. Children in the corresponding age ranges (typically 8-12) have been successfully scanned without adverse effects at the NYU Langone Medical Center and at numerous other research facilities.

Racial and Ethnic Origin

All races and ethnic origins are eligible. Based on prior studies, we expect approximately 25% of participants to self-identify as Hispanic/Latino, and racial composition of participants to be approximately 62% Caucasian, 24% African American, 4% Asian, 1% American Indian, and 9% Other.

Inclusion Criteria

- Student in grades 3-5 of elementary school having one main teacher corresponding to ages between 8 and 12 years-of-age
- Children may be designated as obtaining special education assistance as indicated on an Individualized Education Program (IEP), provided a review of the current IEP by the research team under the supervision of the PI indicates that the child has a broadly average reading level and language development.

- Written assent by child and consent by parent or legal guardian
- IQ: Estimated full scale IQ ≥ 85 and language comprehension standard scores ≥ 8 is required as in past studies to assure that children are able to comply with specific skills training and to minimize neurobiological heterogeneity
- Organizational skills deficits defined as elevated (≥ 1SD) pre-treatment COSS Parent Total T-score and at least one COSS Parent Interference item rated as either a 3 or 4 (indicating an above-average level of impairment)
- Handedness: given the greater prevalence of non-right-handedness in neurodevelopmental disorders, we will track handedness but not exclude left-handed individuals
- Medication: To minimize variability due to medication effects, we will preferentially recruit currently unmedicated individuals (no psychotropic medications in the previous month). For allowed medications, we will require that dosage be stable for >2 weeks before study entry
- Must provide adequate MRI data at baseline

Exclusion Criteria

- Enrolled in a self-contained special education classroom or served by a 1:1 paraprofessional in their classroom
- Absence of signed consent by parent or legal guardian
- Children who dissent regardless of parental permission
- Full scale IQ < 85
- Children with a recent (past 6 months) or current history of neuroleptic treatment or current treatment with psychotropic medications other than stimulants, or guanfacine or atomoxetine
- Per history (and medical records if needed) medical illness requiring chronic current treatment
- History of intrathecal chemotherapy or focal cranial irradiation
- Premature birth (< 32 weeks estimated gestational age or birth weight < 1500g)
- History of leukomalacia or static encephalopathy, intracerebral hemorrhage beyond grade 2, other specific or focal neurological or metabolic disorder including epilepsy (except for resolved febrile seizures)
- History of traumatic brain injury
- Contraindication for MRI scanning (metal implants, pacemakers, metal foreign bodies or pregnancy)

Vulnerable Subjects

This study does not involve greater than minimal risk. It enrolls children in 3rd-5th grade (typically between ages 8 and 12). In compliance with IRB standards for research with vulnerable populations, a description of risks and benefits is included in the Risk/Benefit Assessment section. We will not enroll emancipated minors or mature minors and will therefore require written consent by a parent or legal guardian

as well as child assent, in accordance with IRB regulation. We describe the procedure for obtaining consent and assent in the relevant section below.

Methods & Procedures

Methods & Procedures

This study involves the following steps:

1. Pre-screening. Interested parents/legal guardians will speak with study staff over the phone for the purpose of screening *("Telephone_screening_form.doc")* to determine basic inclusionary and exclusionary information. If the parent/legal guardian endorses any exclusionary criteria or fails to endorse inclusionary criteria over the phone, then the study staff will inform them that the study would not be appropriate. If the parent/legal guardian does not endorse any exclusionary criteria and endorses all inclusionary criteria, then the study staff will make the parent COSS forms available to the parent (via mail or if preferred, via secure web-based platforms, e.g., REDCap https://openredcap.nyumc.org/apps/redcap/). If inclusionary criteria are met based on these forms (detailed in the Inclusionary Criteria section), then the screening visit will be booked during which full consent and assent will take place. Only children are subjects; parents (and, if the child's teacher agrees, teachers) are informants on child's behavior, and thus are not study subjects.
2. In-person evaluation visit. The last set of exclusionary and inclusionary information (with the exception of having an MRI scan that provides data meeting our quality criteria) will be gathered at the screening visit. The section **Cognitive Behavioral Measures** details all the assessments to take place during this visit. During the evaluation visit, children will also practice in the MRI simulator (detailed in section **MRI session** below).
3. First MRI visit pre-OST treatment (detailed in section **MRI session** below).
4. If after the MRI visit the child has met all criteria (i.e., data quality on the MRI scan acquired is good), then the child will be assigned to either the No-Wait study arm (i.e., to begin receiving the OST intervention, optimally within 2 weeks of the successful MRI scan) or to the 12-week wait period (Waitlist study arm) at the end of which the subject completes their second MRI scan, and then proceeds to receive OST.
5. OST intervention (detailed in section **OST intervention** below).
6. Second MRI visit: for the treatment arm, this scan is post-OST treatment, optimally within 2 weeks of OST completion (detailed in section **MRI session** below). For the waitlist control condition, this scan is ~12 weeks after their first scan and before proceeding to OST.

Cognitive behavioral measures (identical for both the R61 and R33 phases)

Cognitive capacity for study eligibility will be verified based on full scale IQ ≥ 85 estimated from the two-subtest *Wechsler Abbreviated Scale of Intelligence-2nd ed.*

(WASI-II)[7] (or where indiciated, the equivalent *Wechsler Intelligence Scale for Children-Fifth Edition* (WISC-V*)*[18]) and scores ≥ 8 on *Understanding Spoken Paragraphs*, *Formulated Sentences* scales and for children aged 9.0 and above, the Multiple Meanings Metalinguistic module of the *Clinical Evaluation of Language Fundamentals-5th ed* (CELF)[8]. For visits taking place during the COVID-19 pandemic, to further support social distancing, the cognitive behavioral measures described above will be administered using the digital Pearson's Q-global platform which has been vetted by NYU Langone's MCIT. As supported by Pearson's Technical Reports "Equivalence of Q-interactive™ and Paper Administrations of Cognitive Tasks: WISC®–V" and the "Using the WASI®–II with the WISC®–V"[18], estimating IQ using either the paper or the digital version of either test is equivalent for children in the 9-12 years old range.

Parents (COSS-P) (and teachers, if the child's teacher agrees to be an informant (COSS-T)) will serve as informants (only the child is a study subject) who will provide baseline and outcome ratings. Furthermore, the Homework Problem Checklist (HPCL)[9] and Academic Progress Report (APR)[5] will be collected to assess generalization of OST benefits to progress in school performance.

Additional phenotypic characterization will be obtained to confirm inclusion criteria and enable dimensional brain-behavior analyses using the following widely used instruments.

Psychiatric disorders will be established by clinicians administering the new computerized DSM-5 KSADS-COMP, based on the KSADS-PL,[10] to parents; all symptoms are measured dimensionally on a 4-point scale and scores and notes entered on a computer.

The parent (and, if the teacher agrees to be an informant, the teacher) *Strengths and Weaknesses of ADHD Symptoms and Normal Behavior* (SWAN)[11] provide dimensional measures of inattention, hyperactivity and oppositionality.

The *Wechsler Individual Achievement Test-3rd ed.* (WIAT-III) is an abbreviated assessment of spelling, mathematics and reading achievement. The *Vineland Adaptive Behavior Scales, Third Edition* (Vineland-3)[12] is a parent interview of adaptive skills.

Besides interviews, parents will complete questionnaires. The *Social Responsiveness Scale-2* (SRS-2) is a widely used dimensional index of autism spectrum disorder (ASD). To assess psychopathology using empirically validated instruments in widespread use, we will include the parent *Child Behavior Checklist* (CBCL).[13]

The *Family Environment Scale* (FES) will be obtained to quantify family conflict.[14] *Hollingshead Index of Social Status*[15] (for comparability with other studies), family

income,[16] birth-date, sex, race, and ethnicity will also be collected as part of the demographic questionnaires.

Pre- and post-intervention administrations of the Cogstate Brief Battery[17] https://cogstate.com/featured-batteries/cogstate-brief-battery/ will also be adopted.

In response to encouragement from funding agency program staff, the Clinical Global Impressions scale will be included before and after completion of OST.

The Biber Cognitive Estimation Test (questions uploaded on research navigator) will more directly capture potential difficulties in estimating time and quantities.

OST intervention

We will deliver OST targeting three core organizational skills domains – Tracking Assignments, Managing Materials and Time Management – in a program consisting of sessions over 12 weeks, each training lasting about 1 hour, and corresponding 30-60 minute weekly review sessions with the parent and the child, 2-3 days following each training session. Sessions will take place remotely by an encrypted video call (i.e., via WebEx secure, encrypted online link accessible on mobile, desktop and tablet devices https://cisco-support.webex.com/guest/articles/en_US/Usability_FAQs/WBX70618/). The review sessions will allow more timely feedback by the therapist regarding content or implementation questions that may have arisen after the training session. If the child and parent report no difficulties practicing the new skill, the therapist will reinforce continued reporting of child's progress.

As typical in the field, to ensure the fidelity of OST treatment implementation, before commencing the study we will first train therapists to deliver the OST program. Training cases will not undergo the MRI scanning, which decreases time-commitment burden to the families. Furthermore, children with contraindications for MRI scanning (metal in the body, such as braces) would be therefore eligible to receive the OST program. Notably, the potential benefit of this study is in the OST intervention; therefore training cases still receive the maximum potential benefit as the study participants who receive the MRI and the OST.

MRI session

Within a week prior to the MRI session, children will be familiarized with the scanner environment by playing a computer game while lying down in a colorfully decorated MRI scanner simulator at the Child Study Center. A *Social Story* will be read aloud to prepare the child for the scanning experience. Our team has a long track-record of obtaining high-quality imaging data in neurodevelopmental disorders, including ADHD and autism, with children as young as 5 years old.

Imaging will be performed using a research-dedicated 3T Siemens Prisma MRI scanner with a 32-channel Siemens head/neck coil, both of which have been FDA-approved for clinical and research scans as minimal risk devices. No exogenous

contrast agent will be used in any imaging sequence. At the beginning of the scan session, participants will be familiarized with the scanning environment and the research team, while the imaging procedures are being carefully explained. The *Social Story* will be read aloud again. The research staff will conduct a metal screening interview with the parent(s) to ensure MRI safety, and will use a hand-held metal detector to search for any metal on the participant (and the parent if they plan on entering the scanner suite while the child is being set-up). Additionally, female participants who have begun menstruation (extremely rare occurrence in our targeted age range) will be instructed to take a urine pregnancy test to ensure lack of pregnancy. If there are no contraindications, participants will be brought into the MRI room. The research staff will place earplugs, headphones, pneumatic belt, and finger transducer (see below) on the child and have him or her lay down on the scanner table. The participant will be positioned on their back on the scanner gantry with head straight aligned with the middle of the coil. The radio frequency imaging coil, which obtains the imaging data, will be positioned in front of the child's face. All participants will be asked to limit head motion. Foam padding will be used for comfort and to comfortably restrict head motion. Once the child is comfortable, we will slide the scanner table into the magnet and begin scanning. Between each scan, the child will be in contact with the research staff through a microphone mounted in the MRI scanner. While scanning is on it gets loud, thus the speaker is turned off and we will not be able to hear the child. This is why the child will have a handheld squeeze-ball device to let the operator know if s/he wishes to immediately stop scanning and be removed from the magnet. The MRI scan can be stopped at any time at her/his request; when s/he squeezes the squeeze-ball, it emits a loud sound in the operator room to notify the research staff who will immediately stop the scan. We spend time during the mock MRI to instruct and coach the child of these procedures so s/he will be prepared before the MRI scan.

Data Analysis and Data Monitoring

Data Analysis

Our primary scientific target is iFC between dorsal anterior cingulate cortex (dACC) and anterior ventral striatum (aVS). Specifically, we will calculate the effect size of the decrease from pre- to post-treatment in dACC-aVS iFC, and will assess the amount of variance in improvement in parent COSS total T-scores that is explained by the change in iFC between dACC and aVS_{FP} (i.e., within the subset of voxels in aVS mask corresponding to the FP subregion: https://osf.io/5m5sx/).

Statistical Plan

This study is funded by a phased innovation application (RFA-MH-16-406), which entails an initial (R61) open phase of two years for milestone-driven testing of our neural target (*dACC-aVS iFC*) of OST intervention. Accordingly, as mandated by NIH, the R61 design is focused on estimating effect size of target engagement (as opposed to conventional hypothesis testing).

R61 phase: The statistical plan, supervised by expert biostatistician Dr. Eva Petkova, a staff member on this study, was created in light of the required design for the R61 mechanism. Specifically, the corrected effect size Hedges g_s (i.e., Cohen's d x 0.98) of change in pre- vs. post-OST-m in *dACC-aVS* iFC were computed. Second, we calculated the correlation between *dACC-aVS$_{FP}$* iFC and improvement in COSS-P total T-score. Our milestones for proceeding to the R33 phase (1) an effect size of ≥ 0.4 in the change from pre- to post-OST-m in *dACC-aVS* iFC **and** (2) the change in *dACC-aVS$_{FP}$* iFC from pre- to post-treatment to account for ≥ 10% of variance of the improvement in COSS-P total T-score were met resulting in proceeding to the R66 phase.

R33 phase. ***Aim 1 H1*** *(time 1 vs. time 2 dACC-aVS iFC will differ between the group receiving OST and the WL group).*

R33 phase data will be collected using the identical experimental protocol used in the R61, therefore we will aggregate across phases to increase power whenever possible. To safeguard against inflating type I errors, we will adopt a "dynamic borrowing" Bayesian approach by assigning weight to the R61 data depending on convergence across the two phases.[2] The Bayesian estimation will be implemented in the R package "BEST v0.4.0"[7] available at https://CRAN.R-project.org/package=BEST. Thus, the effective sample size[8] of the OST group will range from ≥43 to ≥65 individuals, while the WL group will comprise ≥43 individuals.

Analyses testing H1 will utilize the data from all subjects (comprising the samples derived from the Bayesian dynamic borrowing) in a linear model for *dACC-aVS* iFC as a function of treatment (OST vs. WL) and controlling for baseline iFC, age and sex. A significant regression coefficient for treatment would indicate that the post-treatment iFC measure differs between those who received OST and those on WL. Detectable effects: with estimated sample size of 65 for OST, there is 80% power at α=0.05 (2-tailed) to detect a difference between OST and WL of magnitude Cohen's d=0.56. With an estimated sample size of 43 for OST, the detectable effect is d=0.61. Such a medium to large effect size is considered clinically significant.

Aim 2 H2, H3a, H3b *(dACC-aVS$_{FP}$ iFC changes will mediate changes in clinical and academic measures).*
The Sobel mediation test[9, 10] in SPSS[11] will be employed to evaluate these relationships. With 86 children power =80% at $\alpha=0.05_{(2\text{-t})}$ to detect r=0.3, between change in iFC and change in COSS, ~10% explained variance. Power =80% at α=0.05 to detect a d=0.61 effect with n_{OST}=43 (or d=0.56, if effective n_{OST}=65).

Data Safety Monitoring

Consistent with the conclusion that MRI studies do not entail greater than minimal risk, in 10 years of fMRI studies of children and adults, we have never had any reportable events. Nevertheless, as required, we outline our data safety monitoring plan:

Types of Data or Events

Two types of data will be collected:

Interviews and psychological tests. The proposed tests have been used for decades with millions of children. There are no physical hazards associated with interviews or cognitive testing. Our team is experienced in assessing young children with developmental disorders in sessions lasting up to several hours. Sessions are paced with breaks, snacks and physical activities as needed by each child. If the child becomes tired, we reschedule in collaboration with the family. While we strive for collecting complete data from each child, we may defer collecting some measures or even forgo collecting some on a case by case basis.

MRI sessions. MRI scans have long been held to be a safe way to noninvasively visualize tissue in adults and children. This study will be performed on an FDA approved 3-Tesla research dedicated Prisma scanner. The magnetic fields, at the strengths used, are considered harmless and our MRI scanning procedures fall within the FDA guidelines for radiofrequency and electromagnetic field exposure. There are no known significant risks or side effects associated with MRI procedures except the risk of metallic projectiles in the magnetic field or metallic objects in the body. Therefore, participants and their accompanying parent(s) will be carefully screened for previous exposure to metallic fragments or for implanted devices such as electrically, magnetically, or mechanically activated implants (e.g., cardiac pacemakers), clips on blood vessels in their brain, or other metallic objects in their body, e.g., shrapnel, bullets, buckshot, or metal fragments. They will also be asked to place all metallic and magnetic objects in their possession (e.g., keys, jewelry) outside the magnet room.

The risk associated with collection of these data is minimal, and is also described in detail in the Risk section.

Monitoring and reporting

The principal investigator, co-investigator(s), other faculty/staff, and clinical research coordinators will ensure all procedures are conducted according to safety guidelines. We will monitor all participants during evaluations and scanning and be available to participants/parents for any follow-up that may be required. Any unexpected, severe adverse events will be reported to the IRB within 10 calendar days.

Assessments

Given the above information, risk will be monitored in an ongoing manner, not through a formal timed assessment. We do not anticipate any unexpected or harmful events.

Data Storage and Confidentiality

To protect confidentiality, each participant's name will be removed from all data and replaced by an ID number. All identifiable information in paper format (e.g., consent and assent forms) will be stored in locked file cabinets. Only research

personnel directly affiliated with this project will have access to data containing protected health information. No portion of data containing protected health information will be released without written permission from the participant's parent(s)/guardian(s), to the extent permitted by law. Identifying codes will be maintained in the secure web application REDCap https://openredcap.nyumc.org/apps/redcap/. All analyses will be linked exclusively to the identifying codes.

This study is being conducted with support from the National Institute of Mental Health (NIMH). In accordance with NIH mandates for increased transparency and open scientific data sharing, phenotypic and imaging data for each individual will be assigned a Global Unique Identifier (GUID) and will be shared NIMH Data Archive (NDA). The GUID is a universal subject ID allowing researchers to share data specific to a study participant without exposing personally identifiable information while still allowing investigators to track participants longitudinally, across multiple research sites and studies. The NIH GUID tool will be employed for GUID generation https://data-archive.nimh.nih.gov/guid. The GUID Tool is software that accepts the personal information of subjects and uses it to create a series of hash codes. These codes are sent to the NIH GUID system and checked against the GUID database. If these codes have been seen before, that means the information matches an existing GUID and this GUID is sent back. If no match is found, a new GUID is created and sent back. If someone else enters the same information later, the tool will detect this match and send back the same GUID. The GUID itself is a series of alpha-numeric characters. The information required for GUID generation is subject's sex, first name, last name, middle name, date of birth, and city/municipality of birth. All of these items are entered as they appear on the birth certificate, ensuring that the information will not change throughout an individual's lifespan.

Clinical trial registration

This study meets NIH criteria of a clinical trial and accordingly has been registered on Clincaltrials.gov.

Risk/Benefit Assessment

Risk

Potential Risks to Subjects and Provisions for Treatment of Adverse Events

We expect no adverse events. Nonetheless, as detailed here, we will monitor all participants during evaluations, treatment, and scanning and be available to parents/guardians for any follow-up that may be required. Any unexpected, serious, or severe adverse events will be reported to the IRB within 10 calendar days as per NIH policy.

MRI scans: MRI scans are considered a safe way to noninvasively visualize tissue in adults and children. This study will be performed on a FDA approved Siemens Prisma scanner. The magnetic fields, at the strengths used, are considered to

represent less than minimal risk and our MRI scanning procedures fall within FDA guidelines for radiofrequency and electromagnetic field exposure. We feel these are safe levels. There are no known significant risks or side effects associated with MRI procedures except the risk of metallic projectiles in the magnetic field or metallic objects in the body. Therefore, participants and their parents/guardians, if they enter the scanning suite, will be carefully screened for previous exposure to metallic fragments and for devices such as electrically, magnetically or mechanically activated implants, e.g., cardiac pacemakers, clips on blood vessels in their brain, or other metallic objects in their body, e.g., shrapnel, bullets, buckshot, or metal fragments. They will also be asked to place all metallic and magnetic objects in their possession (e.g., keys, jewelry, credit cards) in a locker outside the magnet room.

Some participants report mild discomfort when undergoing magnetic resonance scans. Some participants have experienced claustrophobia (fear of enclosed spaces). If they are prone to claustrophobia, they will be asked to notify the researcher in charge of the scan. The MRI scanner makes loud knocking or beeping sounds during imaging; earplugs are provided to reduce this noise. Due to the rapid rate of change of the magnetic gradients during imaging, peripheral nerve stimulation is a possibility. If this happens, participants may feel creeping or tingling sensations, typically along their arms or lower back. Dizziness and nausea may occur if participants move their head rapidly in the bore of the magnet. Finally, there may be some heating from the radio frequency coils, the cables to the coils, and response and physiological monitoring devices. We do not use cables that can conduct electricity in the proximity of participants, and have had no such untoward events in the past.

Participants will also be instructed how to use an emergency handheld device to inform the operator if they feel discomfort, and/or wish to immediately stop scanning and be removed from the magnet. It is worth noting that the MRI scanning environment necessarily predicates the utmost concern for the complete comfort of the participant. We emphasize that even slight discomfort tends to result in participants moving during the scan, which degrades image quality. Therefore, prior to the imaging session, we have participants complete a mock scanner session using an MRI-simulator, and also spend extra time when we place them on the gantry to make sure they are comfortable, and readjust as needed whenever they let us know that they are even slightly uncomfortable. In general, once a participant has gotten over the novelty of entering the magnet bore, and has habituated to the knocking noises, the main issue is boredom, and staying awake for functional scans. Participants are asked to keep their eyes open during resting state scans to facilitate monitoring of wake status. Participants are free to sleep or watch a DVD or listen to music during several of the scanning sequences (e.g., structural scans).

Given that we are using instruments that are calibrated to deliver energy levels judged to be well within safe limits, we expect no adverse events. Nonetheless, we will monitor all participants during scanning and be available for any follow-up that may be required.

Pregnancy-related risks: There are no known risks of MRI scanning to a pregnant participant or to a fetus, but since these scans are being done strictly for research

and not to benefit the participant's medical care, we will not take even minimal chances. We considered excluding girls who have entered menarche, which is still expected to be infrequent in our age range. However, the median age of menarche (onset of menstruation) has been decreasing for many decades, and is lower among Black and Latina girls than among White girls. Given the importance of recruiting a substantial proportion, albeit a minority, of females, and undesirability of excluding individuals from under-represented racial or ethnic groups, we will not exclude girls who have begun menstruating. Accordingly, we will continue the approach we have followed since 2002, at the insistence of NIMH. Specifically, we will check to be sure that participating girls who have begun to menstruate are not pregnant by using a urine pregnancy test prior to the scan. If the test shows that a participating minor female may be pregnant, we will notify her and her parents and cancel the scan. Since minors cannot participate in research studies without their parents' consent, we notify each female minor participant privately in advance that if her pregnancy test is positive, both she and her parents will be informed. As confirmation, we ask that female minor participants sign that they understand this aspect of participating in the study. To avoid putting young people on the spot, we emphasize that prospective participants do not have to give any reasons to decline participation. Information that the urine pregnancy test is required is provided at the time of telephone screening to confirm lack of other MRI contraindications, which we note includes claustrophobia, which is an entirely subjective complaint. In over 15 years of pursuing this approach, we have never had a positive urine pregnancy test, nor had a situation in which a young participant declined to participate because of the pregnancy test. Of course, unexpected events may occur, and a participant may not be aware that she may be at risk of early pregnancy. In such a case, the PI, a board-certified child and adolescent psychiatrist, would be reached prior to informing the participant and her parents, so as to supervise this potentially delicate process.

OST treatment: There is no physical hazard associated with the OST treatment but possible risks include: increased expectations and non-response. First, for some children with a tendency toward anxiety, increased expectations and consequences provided by study interventions may increase anxiety. Study therapists will monitor children for any such concerns and talk with parents about the best way to address this, should it become a concern. Second, some children may not respond to the intervention and become discouraged. If this should occur, the treating clinician will address this issue with the child and parents to help the child deal with this concern.

Tasks and questionnaires: There is no physical hazard associated with the questionnaires or computerized tasks. The participant is not under any obligation to answer any questions that feel uncomfortable to answer during the interview. We will maintain strict confidentiality about all answers, with the only exceptions being the legal requirements to prevent any immediate or future harm to self or others.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information,

documents, or biospecimens that may identify the participant in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the participant's parent/guardian has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if the participant's parent has consented to the disclosure, including for the participant's medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law.

Protection Against Risks

The most likely preventable risk is loss of confidentiality. To protect against this risk, each participant's name will be removed from all data and replaced by an ID number. All identifiable data will be stored in locked file cabinets. The sheet indicating which participant corresponds to which ID number also will be stored in a locked cabinet, but different from the cabinet storing the raw data. Only research personnel directly affiliated with this project will have access to data containing protected health information. No portion of data containing protected health information will be released without written permission from the participant's parent(s), to the extent permitted by law. Identifying codes will be maintained in locked file cabinets and in password-protected encrypted computer files. All analyses will be linked exclusively to the identifying codes.

Regarding the OST intervention, significant psychological and physical side effects are not expected and none were reported in the efficacy trial. Nevertheless, our protection against risks plan includes participants' progress being monitored by regular contacts with parents and teachers. Additionally, clinicians will meet with participants weekly and if changes in a child's level of adjustment or school performance are noted, these will be reviewed immediately with site supervisors, and if necessary, the child and his/her parents will be seen by the study OST supervisor. In case of an emergency, emergency procedures are available by contacting the child and adolescent psychiatric physician on call. If any physical emergencies arise, parents can contact the pediatric emergency service at NYU or 911. As required by NY State Law, any type of abuse or neglect discovered during the course of the study will be reported to the authorities.

For visits taking place during the COVID-19 pandemic the most up-to-date NYU School of Medicine Standard Operating Procedures and CBI Standard Operating Procedures for work with research subjects will be observed. The most current version of the "CBI Standard Operating Procedures During the COVID-19

Pandemic" (v0.3 as of June 23, 2020) involves a combination of individual researcher health-check clearance, researcher contact tracing, personal protective equipment use, and digitized tracking of proper disinfection of the equipment.

When contacting the parents of currently enrolled children, the trained research associate or trained study team member will use the "Current participants phone screen COVID-19 20200817.docx" phone script to discuss current understanding of study risks in the context of the COVID-19 pandemic and family's continued participation. When contacting potential new participants, study team will use the "Telephone script COVID-19 20200817.docx" which details current understanding of study risk in the context of COVID-19.

Potential Benefits to the Subjects

The child may benefit from receiving OST treatment. OST has been shown to help some children with ADHD improve in organization, time management, and planning. For such children, improved organizational behaviors resulted in better parent-child relationships, fewer problems with homework, and improvement in their school functioning. While we cannot guarantee that any particular child will improve in this manner, prior research has found that this treatment resulted in improvements in children's functioning compared to children in a wait-list condition.

There is no benefit from the imaging aspects of the study, which are being performed for scientific reasons.

Investigators' Qualifications & Experience

All research personnel have completed training in the protection of human subjects.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

We will seek referrals from NYU Child Study Center Clinical Services, local school counselors and clinicians. We will disseminate flyers describing our study to pediatricians and an established network of behavioral therapists, child psychologists and psychiatrists specializing in neurodevelopmental disorders. Study ads have been updated to reflect the change to virual and hybrid (in-person/virtual) education (17-00263 Ad Text2 20200730 tracked; 17-00263 Ad Text3 20200730 tracked; 17-00263 Ad Text5 20200730 tracked). In the past, these IRB-approved ads posted to the Child Study Center newsletter have proven effective in reaching out eligible participants. The study has also been posted on the NYU clinical trials website https://clinicaltrials.med.nyu.edu/clinicaltrial/1204/brain-plasticity-underlying-acquisition/?qd=43871. Additional recruitment approaches include social media (e.g., Facebook Click ads), ads purchased on traditional media and local parent

organizations. As typical for new recruiting studies at NYU, a webpage with our study's description will also be used for recruitment. Since the current study seeks children with impairments in a specific domain, our webpage will provide a brief definition on the webpage along with an optional informational quiz to help better inform any potential participants about the specific deficits we mean by the phrase "*organizational skills*". Accordingly, our recruitment webpage will include an optional organizational skills informational quiz "17-00263_Optional_Informational_Quiz_20170830.docx". This quiz is optional and completely anonymous (i.e., no PHI or IP address information is recorded) and any potential participants who contact us following taking the quiz are under no obligation to inform us whether or not they have taken the optional informational quiz. We have existing research databases at NYU with permission to contact parents of children previously diagnosed with neurodevelopmental disorders (e.g., at NYU, ~180 children with a primary diagnosis of ASD and ~145 with a primary diagnosis of ADHD will be within the target age-range during the project period) "*Telephone script COVID-19 20200817.docx"* details the explanation of the study by research staff and outlines also the scenario when interested families call the Child Study Center to enquire about our study. Additionally, we will employ an EHR query through NYU Langone Health's DataCore for individuals with an ADHD diagnosis and/or medication to treat inattention and use the currently approved (17-00263 direct mail recruitment notification.pdf). Finally, we consistently find that ~20% of our referrals come from word-of-mouth due to our excellent relationships with families and the professional community.

Interested parents/legal guardians will first speak with study staff over the phone who will perform a phone screen to determine basic inclusionary and exclusionary information. If the parent/legal guardian endorses any exclusionary criteria or fails to endorse inclusionary criteria over the phone, then the study staff will inform them that the study would not be appropriate and provide referrals. If the parent/legal guardian does not endorse any exclusionary criteria and endorses all inclusionary criteria, then the study staff will send the parent COSS forms. If inclusionary criteria are met based on these forms (detailed in the Inclusionary Criteria section), then the screening visit will be booked where full consent and assent will take place. The last set of exclusionary and inclusionary information (with the exception of the passing MRI scan) will be gathered at the screening visit. If after the MRI visit the child has met all criteria, then the child will be randomly assigned to receive the OST intervention either within 2 weeks of the successful MRI scan or after a 12-week wait period and their second MRI scan.

Information obtained for children who do not meet inclusion criteria, or who meet exclusion criteria, will be discarded immediately.

Process of Consent

Only children are research subjects in this study. The parents and teachers are informants on child's behavior and not research participants. Members of the research staff will provide parents/legal guardians with information about the study. During this time a member of the research team will carefully review the

consent/assent document, outline the procedure for the study, explain potential risks and answer any questions. The study personnel member who is obtaining consent will also sign to indicate that they reviewed the entire consent form with the parents/legal guardians. The consenting process is continuous, and parents/legal guardians are informed that they may ask questions related to the study at any time. If the participant or parent/legal guardian does not provide written authorization, data corresponding to that participant will not be retained. We only require that one parent/legal guardian sign the consent form, since this is a minimal risk study, it is a burden for most families to have two parents attend the visits, and some children live in one-parent households.

Children will be asked to provide formal assent to participate in the study. The process for determining eligibility to assent is outlined in the section following immediately below. A study personnel member will read the assent document out loud to the child as the child follows along. After each section, the personnel member will ask if the child has any questions, and will also ask the child questions to assess their understanding of the study.

Due to COVID-19 and to keep the safety of both our research team and research subjects, consent and assent will be conducted remotely via an encrypted call (nyumc.WebEx.com, using a secure, encrypted online link accessible on mobile, desktop and tablet devices). A trained research assistant or study staff will schedule a time with eligible interested families to go over the written consent over the encrypted call. Research assistants will email or mail a copy of the consent to participants in preparation for remote consent. After going over the written consent, research assistants will also email the consent via a REDCap link where the participant has the opportunity to read a copy of the written consent and sign electronically, confirming that they read and understood the consent. Research assistants will also document in REDCap the time and date of the remote consent and note that the consent process was done via encrypted call due to COVID-19. The completed informed consent and assent forms will be returned via REDCap.

To preserve equitable treatment of study's subjects, children from public and private schools will be considered for enrollment.

Teachers who work for a New York City public school or teachers who decline to provide research behavioral ratings of their student will be asked by the child's parent or guardian to communicate with the OST therapist in their capacity as the child's main educator.

Teachers who are willing to provide research data in support of the study will be consented over the phone (using Teacher Telephone Consent 20200730 tracked.pdf) or over encrypted video call if the teacher prefers that option. Study staff member will review the Teacher Phone Consent (Teacher Telephone Consent 20200730 tracked.pdf) and address any questions the teacher has. Consent will be

signed electronically using REDCap secure data-capture software in the form Teacher Letter of Understanding 20200730 tracked.pdf.

Subject Capacity and Subject/Representative Comprehension

A requirement to participate in the study is that research subjects have sufficient cognitive abilities and language comprehension to understand the study procedure including OST treatment. This is determined based on any available prior records, history of academic placement and observation at enrollment. The appropriate for this age group written assent form will be provided. A detailed verbal description of the study is also provided explaining what they will be doing and about how long each component will take. Whenever a child indicates they are not willing to proceed with any specific portion of the study, we suspend research procedures. We repeatedly inform children and their parents that we are unable to obtain any research data without the full and continuously provided assent of the child.

Consent Forms

As in our prior imaging studies conducted at the NYU Langone Medical Center and the NYU Center of Brain Imaging, our consent forms follow a standard template and changes will be approved by the Center for Brain Imaging, New York University and the NYU School of Medicine.

Documentation of Consent

Consent documentation was described in the Process of Consent section. Participants and parents/guardians will receive a copy of the signed consent and assent forms. The consent and assent documents are stored in the secure REDCap data capture platform (https://openredcap.nyumc.org/apps/redcap/). Only approved study personnel members will have access to these records.

Costs to the Subject

There is no cost to participate in this research study.

Payment for Participation

Subject to IRB approval, participants will be compensated $75 for the in-person evaluation and $75 for each of the two scanning sessions. We will also offer reimbursement for transportation via public transit for up to 2 individuals, round trip, for each in-person visit, whenever requested on the basis of financial hardship.

Study management and personnel

The proposed study will be executed by the following study personnel:

Responsibility Key:

A) Participant Recruitment and Screening
B) Obtains Informed Consent/Assent
C) Performs Study Assessments

D) Quality Assurance of Assessment Data
E) Performs MRI Scans
F) Quality Assurance of Imaging Data
G) Assessment of eligibility to proceed to Organizational Skills Training
H) Performs Organizational Skills Training
I) Performs Assessments of Outcomes at mid-point and end of treatment
J) Quality Assurance of Outcome Data
K) Data Management
L) Regulatory Reporting and Paperwork Maintenance
M) Integrative Data Analyses

1) Principal investigator:

i. Francisco Xavier Castellanos - Oversees/conducts tasks from A to M

2) Co-Investigator(s):

i. Richard Gallagher - Oversees/conducts tasks from A to M
ii. Yuliya Yoncheva – Oversees/conducts tasks from A to M

3) Other Study Staff:

A) Clinical Evaluators and therapists:

i. Maleeha Haroon - A, B, C, D, E, F, G, H, I, J, K, M
ii. Samuel Jackson – H
iii. Emily Kalver – H
iv. Farah Mahmud – H
v. Julianna Treene – H
vi. Allison Parente – H

B) Research Coordinator: N/A

C) Other Faculty/Research Scientists/Imaging Specialists:

i. Hyung Park – M
ii. Rebecca Shalev - M
iii. Howard Abikoff – M
iv. Luis Martinez Agulleiro – A, B, C, D, F, G, I, J, K, M

D) Research Associates:

i. Lauren Robinson - A, B, C, D, E, F, G, I, J, K, L, M

E) Students/interns/volunteers:

i. Firas Zoha – M
ii. Hicran Dogru – M
iii. Angelina Gorbea – J
iv. Xiaoying Jiang – J
v. Grace Zhao – J
vi. Madison Teets – J
vii. Maria Imas – J
viii. Rida Saad – J

4) Non-NYU affiliated Scientific Collaborator

Adriana Di Martino, MD, Child Mind Institute, NY, NY - M

All study personnel have completed all applicable courses in HIPAA and the ethical conduct of research. A Delegation of Duties log will be maintained in the study

regulatory binder, as per http://www.med.nyu.edu/irb/researchers/faq/your-studys-regulatory-binder/study-staff-logs-and-cvs.

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