A Novel Neuromonitoring Guided Cognitive Intervention for Targeted Enhancement of Working Memory

NCT04002167

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1. PURPOSE OF THE STUDY

a. Brief Summary

The purpose of the study is to develop a cognitive training method that is short, effective and engaging.

b. Objectives

We hope to learn how NIRS-based neurofeedback enhance the effectiveness of cognitive training.

c. Rationale for Research in Humans

The purpose of this study is to examine how human subjects can control their cognitive functions using real-time neurofeedback.

2. STUDY PROCEDURES

a. Procedures

Trained students and staff will screen, consent, enroll, assess, and monitor participants through every step of the process.

Neuroimaging includes functional MRI, anatomical MRI, and NIRS. Participant's physiological responses including heart rate and breathing rate, may be measured inside and/or outside of an MRI scan. This may require a belt around the chest or abdomen (to measure respiration), a pulse oximeter to be worn on the finger. Wearable or standalone eye-tracking devices may be used to track participant's eye movement pattern during the training. Particpant's head movement will be recorded during NIRS measurements using an accelerometer in order to improve the quality of neurofeedback.

VR googles may be used for presenting computerized tasks and/or training.

Demographic data will be collected including education level, ethnicity, socioeconomic status and occupational history. Neuropsychological testing includes measures of IQ, executive functioning, memory, language processing and visual-motor integration. We will also include the Tanner staging assessment - which is a self report scale of physical development to assess where the child is in terms of puberty. Psychiatric assessment will also be done to assess for current and previous emotional and behavioral problems.

Participants will undergo the following procedures:

1) Screening: Potential subjects will be screened via telephone interview (see attached Screen document) or email questionnaire (see eScreen). The screening will involve only questions relevant to this study including certain demographic information, medical and developmental history to establish eligibility status.

2) Consent: All eligible participants will undergo informed consent procedures.

3) Neuropsychological Assessment: All participants will be administered a battery of standardized neuropsychological tests as stated above.

4) NIRS and MRI measurements: Participants will undergo functional near- infrared spectroscopy (NIRS) and magnetic resonance imaging (MRI) measurements. No injections or other invasive procedures will be utilized. NIRS and MRI will be used to provide subjects with real-time feedback about their brain activity during cognitive training as well as to measure the participants' brain activity.

5) Intervention: All participants will either undergo cognitive training with neurofeedback via NIRS or be waitlisted. Participants will have 50% chance to undergo the cognitive training with neurofeedback; those in the waitlist group have the option to receive complimentary cognitive training with neurofeedback after completion of the study.

b. Procedure Risks

Neuropsychological assessment is a very low risk procedure and represents the only objective, valid and reliable method for accurately measuring cognitive function in humans. Neuropsychological assessment represents the standard of care for diagnosing cognitive impairments in children and adults.

Neuroimaging assessments using magnetic resonance imaging scans and NIRS are the most accurate and non-invasive, low-risk methods for determining neurobiological function in humans. Near-Infrared Spectroscopy has the additional benefit of not requiring the subject to endure loud noises or confined space for any period of time. This study will not employ any invasive neuroimaging techniques such as injection of contrast agents. MRI scans and NIRS measurements represent the only existing methods for obtaining accurate, in vivo measurements of the human brain.

c. Use of Deception in the Study

N/A

d. Use of Audio and Video Recordings

Video recording will occur. We will archive the data on the CIBSR server, which is housed in the CIBSR facility in the Department of Psychiatry and Behavioral Sciences. We will occasionally use images or footage in scientific presentations, but in such instances all identifying information will be eliminated or occluded. In such presentations, the recordings will be used to demonstrate the nature of the task and of our study procedure. The recordings will remain on the CIBSR secure server in archived form.

e. Alternative Procedures or Courses of Treatment

N/A

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

N/A There are no treatments involved.

g. Study Endpoint(s)

N/A There are no treatments involved.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Cognitive training is an emergent approach for interrogating brain systems and mechanisms (such as neuroplasticity) that are associated with certain cognitive skills and the practice of cognitive skills. Cognitive training promotes several neuroplastic mechanisms in the brain and has been shown to improve cognitive functioning in healthy individuals. While the mechanism underlying these plasticity- related changes in the brain is still unclear, it is speculated that cognitive training enhances individual's cognitive reserve (i.e. brain's ability to perform cognitive tasks) by recruiting either an alternative brain network or through a more efficient utilization of brain networks.

The main goal of cognitive training is to boost a specific cognitive ability/brain mechanism by employing a set of cognitive training paradigms that target a specific cognitive function. In order for the cognitive training to be effective, individuals are usually asked to perform a set of cognitive training paradigms for a long period of time (1 to 6 months, 10 to 300 hours). The question that we arise here is whether we can make a more efficient cognitive training program that is short and effective. This will be realized by designing a training program that assures subjects will use the targeted brain regions during the training.

b. Findings from Past Animal Experiments

Other groups have shown that cognitive training enhances brain activity in animals.

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Customized MRI Scan Equipment
Description:	Some of the RF imaging coils, imaging software and other devices used to conduct scans at the Lucas Center and CNI (Stanford Center for Cognitive and Neurobiological Imaging) are not approved by the FDA.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The customized equipment does not currently exist in the market, hence our characterization of it as investigational. However, it has been tested for safety by highly trained Lucas personnel.
Investigational Device 2	
Name:	W-NIRS
Description:	An investigational, custom-built NIRS system that is wearable/portable and more cost-effective than commercially available NIRS systems. The engineering collaborator moved from Stanford to Vanderbilt and they keep providing with next iterations of the device. Vanderbilt will not be involved in our study and they will not receive data collected at Stanford.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	There is no known risk associated with functional NIRS. The LED sources used in the system operate under IEC/ANSI standards. Theses LEDs expose participants to much less light compared with commercially available laser-based NIRS systems.

b. IDE-Exempt Devices

IND-Exempt Device 1	
Name:	ETG-4000 (Hitachi)
Description:	NIRS technology uses specific wavelengths of light, introduced at the scalp, to enable the noninvasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) in the capillary beds during brain activity.
IND-Exempt Device 2	
Name:	NIRSSport (NIRx Medical Technologies)
Description:	NIRS technology uses specific wavelengths of light, introduced at the scalp, to enable the noninvasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) in the capillary beds during brain activity.
IND-Exempt Device 3	
Name:	ETG 2.0 (SMI)
Description:	SMI Eye Tracking Glasses 2 Wireless (SMI ETG 2w) are a glasses-type eye tracker with full wireless control and live annotations. Instant calibrationless setup and 4+hrs mobile operation with the SMI ETG 2w smart recorder ensure outstanding productivity for mobile eye tracking research.
IND-Exempt Device 4	
Name:	VIVE (HTC)
Description:	Commercially available VR Goggles and related cameras for presenting the computerized exercises/games in an immersive VR environment.
IND-Exempt Device 5	
Name:	Gear VR
Description:	Commercially available VR Goggles and related cameras for presenting the computerized exercises/games in an immersive VR environment.
IND-Exempt Device 6	
Name:	NIR Scout (NIRx Medical Technologies)
Description:	NIRS technology uses specific wavelengths of light, introduced at the scalp, to enable the noninvasive measurement of changes in the relative ratios of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) in the capillary beds during brain activity.

5. PARTICIPANT POPULATION

a. Planned Enrollment

This research study is looking for 160 participants with ADHD.

b. Age, Gender, and Ethnic Background

Participants (males and females) ages 7-11 years of all ethnic backgrounds will be recruited.

c. Vulnerable Populations

We have already tested the efficacy of the proposed cognitive training in healthy young adults in previous phases of the study. We will be studying minors because, in the future, neurofeedback and cognitive control paradigms are likely to benefit still-developing minors most, due to the increased plasticity associated with early neurodevelopmental processes. Thus, we hope to specifically address the applicability of neurofeedback scenarios in developing populations. We will be taking special precautions to protect the rights of these minors, including following well-established protocols for parental consent and assent.

d. Rationale for Exclusion of Certain Populations

N/A

e. Stanford Populations

Laboratory personnel and students may be subjects in piloting phases.

f. Healthy Volunteers

Participants will be children with ADHD.

Parents and subjects will be asked to notify research staff immediately if they encounter any problems and participation can be discontinued at any time..

g. Recruitment Details

Subjects will be identified using established recruitment measures used at the Center for Interdisciplinary Brain Sciences Research. These procedures include advertising online, including on ResearchMatch, or in local newspapers and posting notices in public places. These procedures also include email messages to email lists and to potential participants.

h. Eligibility Criteria

i. Inclusion Criteria

Meeting diagnostic criteria for ADHD, determined by a BRIEF Working Memory score >=65. Age range: 7 years - 11 years.

ii. Exclusion Criteria

Presence of contraindications for MRI (orthodontia, vascular stents, metallic ear tubes, metal implants, pregnancy, etc) for those participating in an MRI scan. History of serious medical, neurological or psychiatric illness (except disorders of interest) or sensory impairment.

i. Screening Procedures

Potential participants will be screened for inclusion and exclusion criteria via an online and/or telephone screen (see attachments). Only information necessary to ascertain eligibility will be requested. Because the screening will include questions involving medical history to determine diagnosis of ADHD, a limited waiver of authorization will be requested in section 15.

j. Participation in Multiple Protocols

The screening questionnaire will include a question regarding other study participation. Participants can be enrolled in other studies that do not involve medications or substances which would affect the MRI and NIRS measurements or cognitive interventions. Each case will be evaluated individually prior to enrollment.

k. Payments to Participants

Participants will be provided with up to $300 for their participation. If the participant does not complete the all study visits, he will be reimbursed $20/hr for the portion of the study that he has completed.

l. Costs to Participants

None

m. Planned Duration of the Study

The study will require approximately 5 years to complete. Total time per participant: 10-15 minutes for screening, 30 minutes for consent, 30-60 minutes for each neuropsychological testing session, 1 hour for NIRS (or MRI) measurements. Analysis of participant data will require approximately 18 hours per participant.

6. RISKS

a. Potential Risks

i. Investigational devices

For MRI scans, there is a minimal non-significant risk associated with use of the custom-developed imaging coils, imaging software and other non-FDA approved devices used at the Lucas Center.

For NIRS scans, there is also a minimal non-significant risk associated with the use of a custom-developed cap for holding infrared optodes in place.

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents or chemicals

N/A

iv. Procedures

Neuropsychological testing
NIRS measurements
MRI measurements
Eye Tracking
VR-based cognitive assessments and training

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

See notes about MRI and NIRS risks above. Otherwise N/A

vii. Psychological well-being

There is a slight risk that subjects will experience some anxiety, frustration or distress during the neuropsychological testing and/or NIRS/MRI procedures. However, this will be minimized by training and preparation by clinicians. Any anxiety or distress will be brief and transient and the neuropsychological testing will involve rest breaks to minimize discomfort and the NIRS/MRI measurements can be stopped at any time by the participant.

viii. Economic well-being

There is no known risk to subjects' economic well being.

ix. Social well-being

There is no known risk to subjects' social well being.

x. Overall evaluation of risk

Low

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b. International Research Risk Procedures

N/A

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c. Procedures to Minimize Risk

The consent form for all participants lists all possible risks of the procedures. Research staff administering neuropsychological testing will be trained in clinical assessment including how to recognize and deal appropriately with participant distress. Frequent rest breaks will be included in the assessment protocol to help minimize frustration, fatigue and distress.

Research staff are well trained to use protocols and procedures to ensure that the NIRS and MRI equipments are used correctly to minimize any risks. Subjects are instructed that

they can alert the operator that they need help or need to ask a question by speaking directly to the experimenter during the NIRS/MRI scan.

All data handling procedures will follow HIPAA regulations. For each participant, a folder is created that contains signed consent forms, screening questionnaires and NIRS/MRI logs. This folder serves as a permanent archive of original participant data. Extensive precautions are taken to insure the privacy of participants and the confidentiality of data. Specifically, participant identity is numerically coded on all pages within data folders and in the database. All data folders are kept in confidential, locked files at Stanford University. Only personnel directly associated with the grant have access to these files. Data are entered into the computerized database using only the participant ID number, and without any identifying information that would compromise the identity and confidentiality of the participants. Participant background information including name, gender, ethnicity, and relevant medical and personal information is kept in a centralized, restricted access location. This data handling system is efficient, guarantees confidentiality, and serves research needs expeditiously.

d. Study Conclusion

At the discretion of the protocol director, subjects may be taken out of this study due to unanticipated circumstances. Some possible reasons for withdrawing a subject from the study include: The subject fails to follow instructions or perform specified tasks; The investigator decides that continuation could be harmful to the subject; The subject requires treatment not allowed in the study; The study is cancelled; Other administrative reasons.

The experiment will terminate when all study procedures have been completed or when the participant withdraws from the study. Any Adverse Event will be immediately reported to the Stanford University IRB and the Psychiatry department chair.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

- Consent forms
- AEs, SAEs, SUSARs
- Protocol Deviations
- Progress toward Study endpoint(s)

All AEs will be reported to DSMB, NIMH, and/or IRB in compliance with NIMH Reportable Events Policy Schedule.

ii. Person(s) responsible for Data and Safety Monitoring

Dr. Hosseini (PI) and an independent monitoring committee

iii. Scope and Composition of Monitoring Board

The proposed data and safety monitoring board consists of senior and junior faculty with extensive experience in human subject research and/or clinical practice from

Stanford. DSMB members do not have any involvement and financial interests in the proposed study.

iv. Frequency of DSMB meetings

The DSMB will meet twice a year and will provide a written recommendation to NIMH after each meeting.

v. Specific triggers or stopping rules

We do not expect any AE or SAE associated with the proposed cognitive intervention and therefore we do not expect any stopping rule related to the intervention.

vi. DSMB Reporting

To PI and NIMH

vii. Will the Protocol Director be the only monitoring entity? (Y/N)

No

viii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

Yes

f. Risks to Special Populations

N/A

7. BENEFITS

Participants may benefit indirectly through the information learned in their cognitive and behavioral evaluation as well as cognitive training. We believe this research will aid in the development of an efficient cognitive training method that can be ultimately used for boosting/restoring cognitive functions in individuals with impaired executive functioning.

8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.