PROTOCOL TITLE: Neuromodulation augmented cognitive remediation to improve executive dysfunction in fetal alcohol spectrum disorder
VERSION DATE: 11-2-2017

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Neuromodulation augmented cognitive remediation to improve executive dysfunction in fetal alcohol spectrum disorder

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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ABBREVIATIONS/DEFINITIONS

- PAE: Prenatal Alcohol Exposure
- FASD: Fetal Alcohol Spectrum Disorders
- MRI: Magnetic Resonance Imaging
- tDCS: Transcranial Direct Current Stimulation

STUDY SUMMARY

Study Title	Neuromodulation augmented cognitive remediation to improve executive dysfunction in fetal alcohol spectrum disorder
Study Design	Randomized, double-blind, placebo (sham) trial
Primary Objective	Establish feasibility of tDCS for enhancing the efficacy of cognitive training in FASD youth.
Secondary Objective(s)	
Research Intervention(s)/Investigational Agents	Transcranial direct current stimulation (tDCS) Magnetic Resonance Imaging (MRI)
IND/IDE # (if applicable)	N/A
Investigational Drug Services # (if applicable)	N/A
Study Population	Children and adolescents with Fetal Alcohol Spectrum Disorders
Sample Size (number of participants)	40
Study Duration for Individual Participants	4-8 weeks

1.0 Objectives

1.1 Purpose:

- Aim 1: Characterize the feasibility and tolerability of combined cognitive remediation and tDCS in children ages 10-16 with FASD.
    - Hypothesis 1: Children with FASD will tolerate the procedures and remain in the study with less than 20% dropout over the course of cognitive remediation and tDCS
- Aim 2: Evaluate the potential additive benefits of tDCS to the base cognitive remediation program.
    - Hypothesis 2: Cognitive remediation with active tDCS vs. sham tDCS will result in greater gains over the courses of treatment.
- Aim 3: Examine the brain circuitry changes following the intervention.
    - Resting and task fMRI will demonstrate greater change with active compared with sham tDCS.

2.0 Background

2.1 Significance of Research Question/Purpose:

Prenatal alcohol exposure (PAE) has profound detrimental effects on brain development and, as a result, has permanent consequences for cognition, learning, and behavior. Individuals with Fetal Alcohol Spectrum Disorders (FASD) commonly have a range of neurocognitive impairments that directly lead to practical problems with learning, attention, working memory, task planning/execution, and decision making, among other areas of functioning. Recent data indicate that 2-5% of the U.S. population has FASD (May & Gossage, 2001).

Despite the profound public health burden posed by FASD, there have been very few treatment studies of any sort in this population. Our group conducted the first randomized controlled trials of the nutrient choline as a neurodevelopmental intervention in 2-5 year old children with FASD, in which we demonstrated effects on sequential memory (Wozniak et al., 2015). For older children, a very different neurodevelopmental target is needed, and we have narrowed our focus to "plasticity" (the brain's ability to adapt) as that target.

Our group has recently shown that neuromodulation - in the form of transcranial direct current stimulation (tDCS) - can enhance the brain's plasticity in order to increase the efficiency and generalization of cognitive remediation training (Nienow, MacDonald, & Lim, 2016). This work has been done thus far in schizophrenia, which is also a neurodevelopmental disorder. This approach to intervention has not yet been tested in FASD, a condition in which we know there are brain plasticity abnormalities.

We propose to conduct a first-of-its-kind pilot study to examine the effects of a cognitive remediation training augmented with tDCS in children and adolescents with FASD. Functional magnetic resonance imaging will be collected to provide preliminary data of brain circuitry changes created by this intervention.

2.2 Preliminary Data:

- Engagement of population in clinical trials: The University of Minnesota Fetal Alcohol Spectrum Disorders Clinic (directed by Dr. Christopher Boys) and Research Program (directed by Dr. Jeff Wozniak) evaluates more than 300 children with FASD per year and has recruited 345 participants over the last 6 years (including 84 children ages 2-5 for the choline clinical trial).

- Clinical trial experience: Dr. Wozniak and Dr. Lim have both acquired significant experience designing and conducting randomized controlled trials using novel interventions in clinical populations. Dr. Wozniak has completed two small RCTs using a novel nutritional intervention (choline) in children with FASD. Dr. Lim has completed two studies using tDCS in patients with schizophrenia (Nienow et al., 2016) and clinical impulsivity (in preparation).

- tDCS and cognitive training: Schizophrenia has been demonstrated to have impaired neuronal plasticity (Kantrowitz et al., 2016). Dr. Lim has conducted work testing the use of transcranial direct current stimulation to enhance cognitive training in schizophrenia (Nienow et al., 2016). A design similar to what is being proposed for this study was used; all subjects received cognitive training focused on working memory but were randomized to either active or sham tDCS. Compared with sham tDCS, active tDCS was found to double the effect size of learning on the

trained task and was also found to increase the generalization to untrained tasks.

- The level of stimulation that will be used is between 1.0 to 2.0 mA. This is the range that has been used in other studies of children including a 2014 study of children ages 5 to 12 years with language disorders (Andrade et al., 2014). In that study, no serious adverse events were reported. For some participants tingling, itching, and discomfort were observed in some participants after 10 sessions – but these symptoms immediately resolved upon discontinuation of the tDCS. Furthermore, a comprehensive review of pediatric tDCS studies shows that 1.0 to 2.0 mA stimulation consistently produces either no adverse events or mild tingling, itching, and discomfort as described (Antal et al., 2017).

- Cognitive training and imaging: Drs. Wozniak and Lim have conducted and published multiple neuroimaging studies in FASD (Wozniak et al., 2006, 2016) so have experience in imaging this population. In a study of cognitive training in schizophrenia, we found that working memory training increased activation of the dorsolateral prefrontal cortex (DLPFC) compared with social skills training. This has provided our rationale for our anode placement over the left DPLFC. In a current study of cognitive training involving executive function (set shifting), we scanned subjects before and after 10 intervention sessions. We found that subjects who received active tDCS had a significant increase in thalamo-frontal activity compared to those with sham tDCS. This demonstrates the ability of the cognitive training with active tDCS to change resting brain circuitry.

2.3 Existing Literature:

Prenatal alcohol exposure disrupts plasticity in the developing brain: A number of pre-clinical studies have demonstrated that neuronal plasticity throughout the brain is affected by PAE. For example, as summarized by Medina, (Medina, 2011), PAE has been shown to disrupt long-term potentiation in the hippocampus (Puglia & Valenzuela, 2010), long-term depression in the hippocampus and cerebellum (Servais et al., 2007), and cortical plasticity in primary visual and somatosensory cortex (Medina, Krahe, & Ramoa, 2005). In animal models, these types of developmental disturbances in

neuronal plasticity contribute to abnormalities in learning, memory, visual processing, and other cognitive functions. In fact, approaches to improve neuronal plasticity have been proposed as interventions (Medina, 2011).

Deficits in plasticity result in significant neuropsychological problems related to executive function: Persons with FASD can manifest a wide variety of behavioral and neuropsychological problems depending on the timing and extent of prenatal alcohol exposure (Mattson, Crocker, & Nguyen, 2011). A common neuropsychological finding is impairments in executive functioning - a broad set of skills needed for planning and carrying out of goal directed behavior, including working memory, response inhibition, etc. Impairment in executive functioning has been shown to negatively impact functional outcome in many psychiatric and neurological disorders.

Cognitive training alone has modest effects on working memory in neurodevelopmental disorders:
A common deficit in people with schizophrenia is poor executive functioning in the form of impaired working memory. Medications have not been found to improve executive functioning in schizophrenia. Cognitive training, in which there is repeated drilling of exercises of the impaired function such as working memory, has been shown to improve working memory but with only a modest effect sizes and with considerable subject effort. Another limitation is the limited degree of transfer of improvement from the trained task to untrained task.

Cognitive training alone has modest effects on working memory in FASD: Cognitive training has also been tried in FASD. Kerns et al. (Kerns, Macsween, Vander Wekken, & Gruppuso, 2010) used computer based attention exercises administered by educational assistants, in ten children ages 6-15 years. An average of 16 hours of training was provided over 9 weeks. Significant improvement was noted in several attention measures and there were trend improvements in working memory with effect size of d=0.5. In a study that combined subjects with autism spectrum disorder and FASD (Kerns, Macoun, MacSween, Pei, & Hutchison, 2016), a game designed to target attention and working memory was used in subjects 6-11 years, administered by an educational assistant. Approximately 12 hours of training was provided over a 12 week school period. Significant improvements were noted in attention and working memory. However, since the two groups were merged, the specific effect for those with FASD could not be determined. A

limitation of both of these studies is that neither used a randomized controlled design. The durability of the intervention was also not assessed.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

The primary endpoints will be BrainHQ (Posit Science, San Francisco, CA) task performance measures.

- Learning curves derived from repeated sessions of BrainHQ training will serve as the primary endpoints:
  - Scene Crasher; Mind Bender; Juggle Factor; Eye for Detail; and Divided Attention

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

- Neurocognitive measures will be administered at baseline and again after completion of training:
  - Subtests from the Delis-Kaplan Executive Functioning System (DKEFS)
  - Delis Rating of Executive Functioning (D-REF)
  - NIH Toolbox measures (Flanker, Dimensional Card Sort Test, Picture Sequence Memory Test, and Oral Symbol Digit Test)
- Functional Connectivity analysis of resting-state fMRI data
  - Seed-based functional connectivity measure
  - Graph theoretical analysis of connectivity

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

- We will use transcranial direct current stimulation (tDCS) to stimulate the dorsolateral prefrontal cortex (DLPFC).
- tDCS is a non-invasive brain stimulation technique that can modulate brain connectivity.
- tDCS involves applying a weak electrical current (1 to 2mA) to the scalp via anodal and cathodal electrodes, causing either increases or decreases in cortical excitability, respectively.
- Research has shown in both healthy subjects and patients (e.g. Alzheimer's disease, Parkinson's disease, stroke, and depression) that tDCS has the potential to modulate synaptic strengthening and

neurotransmitter-dependent plasticity underlying changes in behavior and learning (Lang et al., 2005).

4.2 Drug/Device Handling:

- tDCS will be applied with a StarStim Enobio system (Neuroelectrics, Barcelona, Spain) using a bipolar stimulation montage.
- This device has been approved for use in research without an investigational device exemption due to meeting criteria for non-significant risk (NSR).
- In addition, the device has built in safety mechanisms which allow for the immediate cessation of stimulation should the subject become uncomfortable or if the impedance of the stimulation electrodes is too high.
- The current will be administered via two saline soaked sponge electrode sponges during each intervention session, using a current strength of 1.0 to 2.0 mA.
- These administration procedures are in line with other protocols that have outlined the safe use of tDCS in pediatric populations (Antal et al., 2017).
- The tDCS cap and stimulation electrodes/sponges will be washed and disinfected after each intervention session and stored under lock and key in 717 Delaware Street SE.

4.3 IND/IDE: N/A

5.0 Procedures Involved

5.1 Study Design:

- The study will be a randomized, double-blind, placebo (sham) controlled trial.
- Eligible participants will be randomized to treatment or placebo in a 1:1 allocation ratio (n=20 active tDCS, n=20 sham).
- Randomization will be from a computer procedure for randomization and tracking.
- All members of the team will be blinded to assignment.
- A block randomization procedure with variable block sizes will be used to maximize unpredictability of assignment.

5.2 Study Procedures:

- Intervention (active tDCS vs. sham): There will be a total of 6 visits for the study - an initial baseline and intervention visit; four

additional intervention visits and one follow-up visit (within one week of the last intervention session)

- Visit 1: Baseline session; three hour visit.
    a. Obtain consent; conduct safety screen for MRI (15 min)
    b. Baseline MRI scan (45 min)
    c. Baseline cognitive testing (60 min)
    d. First tDCS intervention session (60 min)
        i. 14 minutes set-up
        ii. 46 minutes of cognitive training interleaved with two 13 minute blocks of active or sham tDCS (26 minutes total active/sham tDCS)
- Visits 2-5: tDCS intervention sessions; one hour visits.
    a. 14 minutes set-up
    b. 46 minutes of cognitive training interleaved with two 13 minute blocks of active or sham tDCS (26 minutes total active/sham tDCS)
- Visit 6: Follow-up; two hour visit. Within one week of the last intervention session
    a. Obtain consent/screen for MRI (15 min)
    b. Repeat MRI scan (45 min)
    c. Repeat cognitive testing (60 min)

- Cognitive Training Description (Brain HQ):
    - 46 total minutes of cognitive training using the BrainHQ software (Posit Science, San Francisco, CA) will be completed by each subject in each intervention session.
    - The BrainHQ software includes a number of brain training games which focus on various aspects of attention, reaction time, memory and executive function.
    - Positive findings using the BrainHQ program have been reported in children with ADHD (Mishra, Merzenich, & Sagar, 2013) as well as adults with traumatic brain injury (Lebowitz, Dams O'Connor, & Cantor, 2012).
    - The BrainHQ program allows for real-time monitoring of subject performance and adjusts the difficulty level of individual tasks accordingly.

- Additionally, it allows for quantitative tracking of subject performance over time both within and across intervention sessions.

- tDCS Description:
  - Two 13 minute blocks of active or sham 1.0 to 2.0 mA tDCS will be applied in parallel with cognitive training in each intervention session.
  - A 20 minute block of cognitive training without active or sham tDCS will separate the two 13 minute active or sham tDCS blocks with cognitive training.
  - The sham condition will emulate the sensation of tDCS on the scalp at the beginning and end of each 13 minute stimulation block in order to blind the subject to the intervention type, however, current will not be applied for the remainder of the 13 minute blocks.
  - tDCS will be applied with a StarStim Enobio 8 system (Neuroelectrics, Barcelona, Spain) using a bipolar stimulation montage (anode over the left DLPFC/F3 and cathode over the right orbitofrontal cortex/FP2).
  - The StarStim device allows for double-blinded administration of tDCS/sham stimulation during each session.

- Neuroimaging:
  - Pre- and post-intervention fMRI will be collected to examine resting state connectivity changes and reversal learning task changes.
    a. Subjects will be scanned at the Center for Magnetic Resonance Research on a Siemens Prisma scanner using Human Connectome Project accelerated imaging (Glasser et al., 2016).
    b. A high resolution structural scan and a select period of resting-state fMRI (eyes open and eyes closed) will be collected.
    c. fMRI during a reversal learning task will also be collected. Our group has previously used this task to assess brain function related to cognitive flexibility and executive function.

- Analysis will be done using already published functional connectivity approaches (Haut, Lim, & MacDonald, 2010; Wozniak et al., 2016).

- Assessments: Note that all instruments are to be administered for research purposes (not for clinical diagnostic or treatment purposes). Standard precautions will be implemented to reduce potential frustration and fatigue (frequent breaks, positive feedback about performance, etc.)
  - <u>The following assessments will be administered to the child using the NIH toolbox using an iPad:</u>
    a. NIH Toolbox Flanker Inhibitory Control and Attention Test measures both a participant's attention and inhibitory control. (Heaton et al., 2014)
    b. NIH Toolbox Dimensional Card Sort Test (DCCS) is an assessment to measure of cognitive flexibility.
    c. NIH Toolbox Picture Sequence Memory Test (PSMT) is a measure for use in the assessment of episodic memory.
    d. NIH Toolbox Oral Symbol Digit Test (OSDT) is a measure of processing speed. (Denboer, Nicholls, Corte, & Chestnut, 2014).
  - <u>The following additional assessments will be administered to the child:</u>
    a. Subtests from the Delis-Kaplan Executive Functioning System (DKEFS): a standardized battery of executive functioning.
  - <u>The following questionnaires will be administered to the parent:</u>
    a. Parent and Child Questionnaire
    b. Behavior Assessment System for Children – 3rd Edition (BASC-3): a standardized parent-report questionnaire of typical and atypical child behavior.
    c. Delis Rating of Executive Functioning (D-REF): a standardized parent-report questionnaire of child planning, organization, attention, inhibition, and emotional control.
  - <u>The tDCS Report of Symptoms questionnaire will be administered to the child before and after each tDCS/sham intervention:</u>

a. Assessment tool to monitor for common, specific side effects noted across many existing tDCS studies, including but not limited to itching, prickling, burning sensation, nausea, fatigue and headache.
b. Approximately 3-5 minutes to administer and is typically performed twice during each intervention session (once before and once after the session).
c. Furthermore, participants will be continuously monitored by a member of the study staff throughout each intervention session to ensure comfort and safety.
d. In addition, at the end of each intervention visit, the subject will be asked if they think they received the active or sham condition.

- All forms are attached to this submission

5.3 Follow-Up: Participants will be contacted by phone 30 days after the last intervention session. The tDCS Report of Symptoms questionnaire will be administered.

5.4 Individually Identifiable Health Information: See attached HIPCO Ancillary Review Form and HIPAA Authorization form

5.5 Use of radiation: NA – neither MRI nor tDCS uses ionizing radiation

5.6 Use of Center for Magnetic Resonance Research: This study uses the CMRR and follows all CMRR protocols and procedures.

6.0 Data and Specimen Banking

6.1 Storage and Access: Storage and Access: De-identified neuroimaging data will be stored locally on servers supported by the Center for Magnetic Resonance (CMRR). De-identified cognitive and behavioral data will be stored in a secure, HIPAA-compliant RedCap database supported by the university of Minnesota.

6.2 Data: Data elements to be stored will include processed, de-identified neuroimaging results (ex. regional brain volumes, measures of white matter integrity, and measures of brain connectivity), de-identified neurocognitive test results, and de-identified behavioral questionnaire data.

6.3 Release/Sharing: Release/Sharing: There are no plans to share these data with outside entities.

7.0 Sharing of Results with Participants

7.1 Standardized neurocognitive test results may be shared with participants' parents if requested. Dr. Wozniak is a clinical neuropsychologist with 20 years of experience providing clinical neuropsychological information to parents. This will be done in an ethical manner, sharing only the necessary data and not interpreting it clinically but, rather, passing on standardized scores in a manner consistent with American Psychological Association ethical standards. Neuroimaging results are not shared with participants with the exception of a single "souvenir image". If a potential abnormality is identified in the MRI scan and the radiologist review indicates that a clinical follow-up is needed, a full set of images will be prepared on a DVD for sharing with the clinician doing the follow-up.

8.0 Study Duration

8.1 Describe:

- Participants will complete the 6 visits described above, typically within a span of 8 weeks maximum.
- All study participants will be enrolled within the two year timeframe of the study.
- Data analysis is expected to continue for 1-2 years post study conclusion.

9.0 Study Population

9.1 Inclusion Criteria:

- Documented heavy prenatal alcohol exposure (self-report, social service records, or adoption records) and meeting criteria for an associated FASD diagnosis (FAS, partial FAS, or ARND).
- An available parent or legal guardian capable of giving informed consent

9.2 Exclusion Criteria:

- All participants: Substance abuse in the participant; Neurological condition or other developmental disorder; Serious psychiatric disorder known to effect brain functioning and cognitive performance; Birthweight < 1500 grams; MRI contraindication, tDCS contraindication.

9.3 Screening: Participants will be screened by telephone using the attached screening tool.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☒ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

10.2 Adults lacking capacity to consent and/or adults with diminished capacity to consent:

- N/A

10.3 Additional Safeguards:

- Children and adolescents are the focus of this study because it is a study of the neurodevelopmental effects of prenatal alcohol exposure and the desired outcome is to learn more about the presentation of effects over the course of development. Children and adolescents will all undergo a formal assent process at the same time as the parent undergoes a formal informed consent process. Children who are wards of the state will not be enrolled.

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: Up to 60 participants will be consented in this study, with the goal of having 40 participants enroll and complete the full study.

12.0 Local Recruitment Methods

12.1 Recruitment Process: Families of potential participants will be contacted by research staff or will initiate contact themselves. Visitors to the clinics described below may see flyers and brochures describing the study at the time of their clinic appointment although they will not be recruited directly by their clinician. Mailings will also be sent to families of children with FASD via lists provided by the Minnesota Organization on Fetal Alcohol Syndrome (MOFAS). MOFAS has close working relationships with Dr. Wozniak, Dr. Eckerle, Dr. Boys, Dr. Gross and both clinics. All recruitment materials will be submitted for IRB approval upon development, before use in the study. Telephone scripts will be utilized.

12.2 Source of Participants: Participants will be recruited from two University of Minnesota Medical Center Clinics in which co-investigators see patients: The Fetal Alcohol Spectrum Disorders clinic (Dr. Christopher Boys, Ph.D., Dr. Amy Gross, Ph.D) and the International Adoption Clinic (directed by Dr. Judith Eckerle, M.D.).

12.3 Identification of Potential Participants: Potential participants will self-identify in some cases based on advertisements. In other cases, participants will be recruited based on having been seen for an evaluation for FASD. Participants will not be recruited by a clinician (to avoid potential coercion and/or confusion about clinical care vs. research. Instead, research staff will contact families and will conduct telephone screens to determine eligibility. Access to contact information for potential participants will be obtained from the clinicians who are co-investigators on the study (Dr. Boys, Dr. Gross, and Dr. Eckerle). Patients who "opted out" of allowing their clinical data to be utilized for research via the standard UMMC / Fairview clinical consent form will not be recruited.

12.4 Recruitment Materials: See attached recruitment materials in ETHOS.

12.5 Payment: Participant families will receive payment (check or pre-paid card) for participation. Because the participants are children, the payment will be provided to the parent on behalf of the child. Payment will be made at the completion of the study (final visit) or at the time of a participant dropping out of the study. Payment will be based on procedures attempted and/or completed as follows:

- $50 for the neuropsychological testing and parent rating forms
- $50 for each MRI scan ($100 total)
- $25 for each tDCS session ($125 total)

- The maximum payment per participant will be $275.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Participants may withdraw or be withdrawn from the study at any point. Participants may be withdrawn for MRI contraindications (ex. metal implanted in body between visit 1 and 2), tDCS contraindications (ex. seizures, brain trauma), failure to complete study procedures, or loss to follow-up.

13.2 Withdrawal Procedures: Participants who withdraw or are withdrawn from the study will not be followed further. Payment will be provided for all attempted and/or completed procedures.

13.3 Termination Procedures: Data collected prior to withdrawal may be used from withdrawn participants.

14.0 Risks to Participants

14.1 Foreseeable Risks:
The risks of MRI are as follows:

- Projectiles: Objects with magnetic properties can be pulled into the magnet and turn into projectiles. To minimize this risk we ask that subjects remove all metallic items (watches, cell phones, hair pins, etc.) prior to entering the scanner and by controlling access to the scanner.
- Claustrophobia: The scanner is a long narrow tube that may cause some people to feel claustrophobic.
- Hearing Damage: The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage if you do not wear hearing protection. Hearing protection is required and is provided by the investigator.
- Nerve Stimulation: Some people experience localized tingling, twitching, or muscle contractions during MRI scans. This is expected, but if it is uncomfortable, the scan can be stopped immediately.
- Disruption of Devices: Some devices can be damaged by magnetic fields and should not be brought into the scanner room. This includes some implanted devices such as pacemakers, cochlear implants, insulin pumps, nerve stimulators, etc. Participants will be screened thoroughly prior to scanning to ensure that they do not have such implanted devices.
- Heating of Devices: The radiofrequency waves used in MRI can heat conductive materials such as metal implants (screws, plates,

rods, wires, artificial joints, etc.), certain tattoo inks, certain clothing fabrics, jewelry, medication patches, wigs, etc. Participants will be asked to remove these items if possible. If they cannot be removed they will be asked to provide more information to allow MRI staff to be able to make determination on the safety of proceeding with the scan.

The approved CMRR screening procedures will be employed prior to scanning. The participant will undergo thorough screening for metal at the time of scheduling and, again, prior to entering the MRI suite. During the scan, the participant will have a squeeze ball to signal a desire to stop the scan and the participant will also be in voice communication with the scanner operator.

The risks of tDCS are as follows:

- This study involves the use of a tDCS device, which is considered to be a safe brain stimulation technique that rarely results in adverse events.
- There is currently no evidence of serious side effects.
- Criteria for discontinuation that may rarely occur are sores at the tDCS administration site, and headaches that temporarily affect comfort / functioning.
- Mild side effects that typically resolve upon discontinuation of tDCS include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea.
- The participant may also choose to discontinue stimulation at any time during the session if experiencing discomfort or side effects.
- No other risks are anticipated. Nonetheless, in order to minimize risks, study staff will be using standards of administration that have been shown to be safe in numerous other studies and across more than 2000 studies (Liebetanz et al., 2009; Nitsche et al., 2007; Poreisz, Boros, Antal, & Paulus, 2007) using tDCS; this includes length of administration, magnitude of the current, size of electrode sponges used, and method of applying stimulation.
- Any unanticipated problems or adverse events will be reported to the IRB

The risks of neurocognitive testing / checklists are as follows:

- Neurocognitive testing can be challenging and tiring. Children will be given ample opportunities for breaks and will be given encouragement to complete tasks to the best of their ability.
- Checklists cover sensitive topics. Participants have the option of skipping items that they are uncomfortable answering.

14.2 Reproduction Risks: There are no known risks to fetuses from MRI, but we will take steps to ensure that no pregnancies are exposed to MRI nonetheless. Parents and participants will be told that the participant should not undergo MRI if there is a pregnancy or the possibility of a pregnancy (i.e. sexual intercourse without effective contraception taking place). There are no known risks to fetuses from tDCS, but we will similarly take steps to ensure that no pregnancies are exposed to tDCS.

14.3 Risks to Others: Parents who accompany children to the MRI facility (CMRR) will be screened as though they will be entering the MRI suite (even though the plan will be for them to remain in the attached control room). All CMRR procedures will be followed in this regard.

15.0 Potential Benefits to Participants

15.1 Potential Benefits: There are no direct benefits for the participant or family. Rather, the research is expected to benefit the population of individuals with FASD through the knowledge acquired.

16.0 Data Management

16.1 Data Analysis Plan: Data analyses will include traditional statistical analyses for group differences in neurocognitive and brain measures with control for confounding variables, multiple comparisons, etc.

16.2 Power Analysis: We propose to compare changes in cognition and in brain circuitry between the two intervention arms. With an n=20, alpha 0.05, power of 0.8, we have power to detect an effect size of 0.9.

16.3 Data Integrity: Neuroimaging data will be subjected to standard quality control measures (both automated and manual) including measuring and controlling for artefacts. Neurocognitive data will be checked for quality by more than one research staff member.

17.0 Confidentiality

17.1 Data Security: Data will be handled by trained research staff members. Paper records will be stored in locked file drawers and electronic data storage will meet University security requirements (password protection, encryption, controlled access, audit trails of access, etc.). Protected Health Information will be separated from research data. Research data will be coded and, thus, de-identified. De-identified data will be stored in a local HIPAA-compliant RedCap database managed by the University of Minnesota. Signed consent forms will be scanned into the OnCore system as required by the University. Research information will not be placed into the individual's electronic medical record.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

N/A - The principal investigator will monitor safety and data quality for this study. They will ensure that adverse events are reported accordingly and that data are generated, documented (recorded), and reported - in compliance with this protocol, with Good Clinical Practice, and any other applicable regulatory requirements.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: Potential participants will not be contacted to inquire about research participation if they have opted out of research as part of signing the standard UMMC/Fairview consent to treatment form. During telephone screening, potential participants will be given multiple opportunities to decline screening and participation in research. During the study itself, participants will be informed that they are free to skip questions on questionnaires or decline to answer interview questions if they find the material too sensitive or uncomfortable. Dr. Wozniak, a licensed clinical psychologist, has worked extensively with patients, families, and research participants over the years and is acutely aware of handling sensitive topics in relation to child mental health and development. He will ensure that all aspects of the study include the consideration of participant comfort and privacy as a top priority.

19.2 Access to Participants: As part of the consenting process, participants will give their formal consent for the study team to collect sensitive information. This will include the signing of a separate HIPAA form granting the study team access to the participant's medical record.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: Compensation for Research-Related Injury: In the event that this research study results in an injury, we will provide treatment including first aid, emergency care, and follow-up as needed. Care for injuries would be billed in the ordinary manner and costs would not be covered by the research study itself.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

- The informed consent process will begin at the time of the telephone screening and will continue throughout participation. During screening, parents will be informed about the purpose of the research, why their child was chosen for possible participation, what the

potential procedures are, and how long they will take, and payment. This will allow them time to formulate questions which could be posed to investigators at the time of the in-person enrollment visit.

- Enrollment will be done in person with the parent(s) providing consent and the child providing assent.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): We are requesting a waiver of documentation of the consent for only the phone screen portion of the study. Participants would be consented prior to any other study activities. We need to collect sensitive information from the parent/guardian prior to the first visit and documented consent process in order to determine basic eligibility. All parents will be read the attached script and asked to verbally consent to the phone screen only.

21.3 Non-English Speaking Participants: Participants will be English speaking.

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

- The participants in this study will be minors (<18 years of age) at the time of enrollment. Parental consent (from one parent) and child assent will be utilized in all cases at enrollment.
- Because this is an intervention, foster children and/or wards of the State will not be enrolled.
- Assent will be obtained from all participants; Assent will be documented with a signed form.

21.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: NA

22.0 Setting

22.1 **<u>Research Sites:</u>**

- Participants will be recruited from the Fetal Alcohol Spectrum Disorders clinic and the International Adoption Clinic at the University of Minnesota.
- Procedures will be performed in the Center for Neurobehavioral Development (CNBD) and the Center for Magnetic Resonance Research (CMRR).

23.0 Multi-Site Research

N/A; single site only

24.0 Resources Available

24.1 Prior studies by our research group, including a previous study with very similar methodology to this one, have demonstrated high interest on the part of

families in participation. Recruitment targets have been met for all previous studies.

24.2 The principal investigator, Dr. Wozniak, will devote approximately 15% effort to the study over the course of the project.

24.3 Facilities include the CMRR (which is ideally set up for neuroimaging work), the CNBD (which is ideally set up for collecting neuropsychological and behavioral data), and the DCRU (which is ideally set up for assisting with biological samples.

24.4 Dr. Wozniak, the principal investigator, is a licensed clinical neuropsychologist with 19 years of experience in managing children and adolescents with developmental disorders and mental health conditions. He has conducted numerous studies in the Academic Health Center and knows how to access resources relevant to clinical research as well as for managing unexpected events.

24.5 Dr. Wozniak will personally ensure that research coordinators are appropriately trained and overseen. Dr. Wozniak's Department (Psychiatry) has a Clinical Research Specialist (Mahyra Johnson) as well as a Regulatory Specialist (Patricia Carstedt) who are available to assist with training and oversight.

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