PROTOCOL TITLE:

Learning enhancement through neurostimulation (LENS)

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

One of the hallmark symptoms of Autism Spectrum Disorder (ASD) is difficulty with social communication and interaction. Although numerous behavioral interventions have been developed to address social difficulties in ASD, one evidence-based social skills training program in particular has demonstrated promise in improving social skills knowledge and social functioning: the UCLA Program for the Education and Enrichment of Relational Skills (PEERS)[1], which is a manualized, evidence-based program for high-functioning adolescents with ASD. Despite the success of this program, not all individuals benefit from social skills training[2]. Reasons for non-responsiveness are likely complex and varied, ranging from differences in neural responsivity, cognitive function, temperament and social support. One neurocognitive factor that may impact social learning is the ability to filter out irrelevant information, or attend to relevant social information [3]. Therefore, targeting selective attention at the neural level may have benefits for social skills learning. Recently, brain stimulation techniques such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have shown promise in enhancing learning, attention and other behavioral outcomes in ASD [4-6].

In the present proposal adolescents with ASD who will receive PEERS training with active or sham tDCS to determine whether social skills training can be enhanced with neuromodulation. tDCS is a minimally invasive neuromodulatory technique that delivers low current through scalp electrodes. tDCS modulates ongoing neural activity by affecting neuronal membrane potential. tDCS has shown some promise in reducing neuropathic pain [7], alleviating symptoms in some psychiatric disorders [8-9] and enhancing motor function following stroke [10]. tDCS was chosen as a neuromodulatory technique in the present proposal due to its portability which is well suited to allow for tDCS to be delivered concomitantly with social skills training, which requires interaction with a group of individuals. Animal studies also suggest that the effects of tDCS stimulation may last beyond the period of stimulation [11].

The aims of this study are to:

- **Aim 1**. Establish the safety and feasibility of administering active and sham tDCS with PEERS training in adolescents with ASD. We predict that tDCS administered with 1.5mA current will be safe for participants and tolerable for the majority of participants.

- **Aim 2**. Examine the impact of tDCS in improving social skills and attention to faces. We predict that active tDCS in conjunction with PEERS training will improve social function and attention to faces to a greater degree than sham tDCS plus PEERS training.

- **Aim 3**. Examine the impact of tDCS on neural correlates of social function and attention to faces using functional magnetic resonance imaging (fMRI). We predict that activity in regions that underlie social behavior (e.g., medial prefrontal cortex, temporoparietal junction, fusiform gyrus, amygdala) will increase more in response to social stimuli following active tDCS with PEERS training compared to sham tDCS with PEERS training.

Impact. The present study will address the need to find approaches to enhance social learning in ASD. Social communication difficulties may become especially apparent during adolescence, a time period marked by greater emphasis on social relationships and peer influence. Therefore, the present strategy is to examine the efficacy of a minimally invasive neuromodulatory technique in adolescents in combination with an evidence-based behavioral intervention, PEERS, to enhance social information processing and social interaction, with fMRI markers of neural plasticity before and after intervention.

2.0 Background

PEERS. PEERS is one of the only empirically supported social skills programs for adolescents with ASD. PEERS utilizes cognitive-behavioral methods to teach social skills[12]. The program specifically targets friendship, relationship development, and decreasing isolation in adolescents[13]. The PEERS intervention consists of 14 weekly 90-minute sessions for adolescents and their parents. Four previous randomized, controlled studies and one quasi-experimental study cited gains in overt social skills, improved quality of friendships, and frequency of peer interactions[1, 13-16], with treatment gains maintained at 14-week follow-up[1].

To date, only one study has investigated neural function in a group of adolescents completing the PEERS program[13]. This study demonstrated a shift from right-hemisphere gamma-band EEG asymmetry to left-hemisphere EEG asymmetry following completion of PEERS. No such changes were noted in typically developing adolescents or in wait-listed ASD participants. In addition, left-dominant EEG-asymmetry at post-test was associated with increased social contacts, knowledge about social skills, and fewer symptoms of ASD. The present study has promising implications for demonstrating that cognitive-behavioral intervention is associated with changes in neural activity in adolescents with ASD.

Only two previous studies have investigated the effect of tDCS on children with ASD. Results indicated improved syntax acquisition following a 30-minute treatment period[4] and decreased autism symptoms and behavioral problems up to seven days post-treatment[17]. Both studies reported that treatment was well-tolerated by participants. Recent reviews have also concluded that tDCS is well tolerated and safe for adolescents [18].

Innovation

This study will be the first of its kind to combine evidence-based social skills treatment (PEERS), with neurostimulation using tDCS and to evaluate treatment outcomes using both behavioral data and fMRI. Should this project establish tDCS as a safe, tolerable and viable neuroenhancement technique, it may be added to other behavioral interventions such as, and extended to younger children, including those receiving intensive early behavioral intervention. In addition, tDCS is a technique used in animal models to improve cognition [19], so it can also be applied to animal models of autism, an area of intense investigation. In summary, the impact of the proposed project is to establish tDCS as a means to enhance social learning and selective attention in ASD. This not only could enrich research efforts, but could also have a broader impact through future integration of this technology into clinical practice.

Preliminary Studies conducted by the research team

Investigator Gwynette and his team are the only PEERS-certified clinicians in SC. Dr. Gwynette has extensive experience with pioneering social skills programs at MUSC as director of Project Rex, a social skills program that has provided treatment for 88 adolescents with ASD and their families in the past two years. In an unpublished analysis of clinical outcomes for thirty-seven adolescents with ASD, participants achieved a mean improvement of 10.42 points on the Social Responsiveness Scale parent total score following treatment.

Investigators Carpenter and Borckardt have previously conducted a brief, IRB-approved feasibility study using tDCS with a child with ASD. Unpublished data demonstrated that the child habituated to the sensation within about 10 minutes, and that he was able to move about and interact freely during a 20-minute stimulation session. Other than slight redness where the forehead electrode was applied, no adverse effects were noted. Co-I Borckardt has conducted numerous studies using tDCS in diverse clinical populations. He will serve as the NCNMR4 Collaborator for this proposal.

Consultant Manuel Casanova has conducted several clinical trials in people with ASD using brain stimulation techniques (primary rTMS). He will provide intellectual input on the overall design of the study and guidance on brain stimulation methodology. He will also be a co-Investigator on any grant applications that result from this pilot award.

PI Joseph conducted an fMRI study [20] in typical and ASD youth to examine neural response to faces and non-faces. They found that the right fusiform gyrus showed a trend toward normal development of face specialization in ASD (i.e., increased fMRI response to faces relative to non-faces with age), but the left amygdala actually showed decreased face specialization with age in ASD. This finding fits in with the EEG finding that it was left hemisphere gamma activity that was associated with improved social skills in ASD following PEERS training[13] and with the case report that tDCS applied to the left dorsolateral prefrontal cortex decreased ASD symptoms[21]. Hence, left-hemisphere structures may show altered response to social information, but PEERS training, tDCS, or the combination, as proposed here, may mitigate this altered responsivity.

3.0 Intervention to be studied (if applicable)

PEERS training will be paired with active or sham tDCS. As described above, PEERS is one of the only empirically supported social skills programs for adolescents with ASD. PEERS utilizes cognitive-behavioral methods to teach social skills[12]. PEERS is a parent-assisted intervention that teaches targeted social skills to high-functioning patients with ASD during fourteen weekly sessions. Parents and adolescents attend separate concurrent sessions that instruct them on key elements about making and keeping friends. Details of the activities that occur during PEERS sessions are provided in the Section 10.0.

tDCS is a brain stimulation technique that uses 1-2mA current applied to the scalp to affect neuronal membrane potential but does not cause neural firing. It is being explored as a therapeutic for a number of neurological and psychiatric disorders, and appears to be promising in terms of enhancing behavioral or treatment response when administered concurrently with behavioral treatments [22-23]. tDCS is still in the early stages in its application to children, with encouraging initial results across disorders and computational models for dosage considerations in a youth population[24]. Previous research has demonstrated that tDCS is well-tolerated and safe for children and adolescents in a Psychiatry setting [18]. It is also tolerated by children with epilepsy with no adverse side-effects and clinically significant decreases in seizure activity for 48 hours post-treatment [25].

As described more in Section 10.0, active tDCS will be administered to half of the participants and sham tDCS will be administered to the other half

tDCS is not an FDA-indicated technique for autism-spectrum disorders and there are no FDA-approved tDCS devices to date. However the Ionto device used for this study is FDA-approved for iontophoresis and is equipped with all relevant current and voltage regulation/safety features. As with most tDCS studies conducted at MUSC, this device will be used off-label for tDCS delivery.

4.0 Study Endpoints (if applicable)

The primary endpoints are changes in responses on various clinical measures pre- and post-intervention: the Social Responsiveness Scale, the Social Skills Improvement System, the Quality of Play Questionnaire, the Aberrant Behavior Checklist, and the Test of Adolescent Social Skills Knowledge-Revised. We predict that participants receiving active tDCS will show greater improvement in these measures compared to those receiving sham tDCS. This will be assessed using non-parametric t-tests (IBM SPSS Statistics, Chicago, IL) conducted separately for each measure.

Secondary endpoints will be fMRI response and reaction time pre- and post-intervention on a laboratory test of attention and social information processing.

The primary safety endpoint will be self-reported adverse effects of tDCS collected after each treatment session.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria for Adolescents:

- Participants in this study will be youths aged 14-17 with a documented history of ASD who are enrolling in a PEERS program at MUSC.
- Participants will be screened for eligibility using the ADOS-2, the gold standard instrument for diagnosing ASD. A score falling with the autism spectrum range on the ADOS-2 is required.
- Participants will also be screened for IQ using the K-BIT2, an IQ measure appropriate for children and adolescents. Subjects must score higher than 70 on the K-BIT2.
- Participants must be willing to enroll in PEERS training and to receive brain stimulation prior to being included in this study

Exclusion Criteria for Adolescents:

- Epilepsy, or a seizure in the last year
- Vagal nerve stimulators
- Participants may continue to take prescribed medications during the course of the treatment. However, no dosage or agent changes may be made one month prior to the study or during the study. If a medical or behavioral treatment change must be made during the course of the study, participation will be discontinued.
- Allergy to benzocaine
- Prior brain stimulation (tDCS, TMS, ECT, DBS) intervention
- Inability or unwillingness of subject or legal guardian/representative to give informed consent
- Non-native English speaker
- Metal pins, plates or clips in the body or orthodontics
- Surgical implants such as pacemakers or cochlear implants
- Permanent makeup or tattoos near the face or head
- Metal fragments in the body (from welding, shrapnel, BB guns) or suspect that they have fragments
- Claustrophobia
- Past closed head injury or concussion
- Currently under the influence of alcohol or other recreational drugs
- Smoker
- Cannot understand the fMRI task instructions
- Cannot lay still in the mock scanner for a period of 5 minutes
- Prior PEERS training

Inclusion Criteria for Parents:

- Have a child with Autism Spectrum Disorder and willingness and ability to participate in the weekly PEERS session

Exclusion Criteria for Parents:

- Enrolled in an academic course in which Drs. Joseph, Gwynette, Carpenter or Borckardt are instructors

No individual will be excluded based on race, gender, or ethnicity. The parent can be either male or female.

Only adolescents from age 12-17 will be included because the study is focused on behavioral and neurostimulation interventions that are expected to enhance social skills. Adolescence is a developmental time period where social information processing is particularly relevant.

6.0 Number of Subjects

A total of 34 subjects will be recruited for the study (17 adolescents and their parent), but a drop-out rate of approximately 40% is expected, leaving 10 adolescent subjects with complete datasets.

7.0 Setting

- The initial visit to MUSC will take place at the Center for Biomedical Imaging (CBI) at 30 Bee Street. Baseline assessments using ADOS-2 and K-BIT2 and tDCS acclimation will take place in a quiet testing room in the CBI facility. Parents will fill out questionnaires in an adjacent area at CBI. These questionnaires will be entered into RedCap and no identifying information will be linked to the survey responses.
- tDCS acclimation, Mock scanner training, and fMRI scanning will also take place at CBI.
- Brain stimulation with active or sham tDCS will take place in the MUSC Institute of Psychiatry South, 5th Floor

8.0 Recruitment Methods

- Recruitment will occur during the first 3 months of the study. Potential subjects will be recruited through the Department of Psychiatry at MUSC and from the greater Charleston area community.
- Potential subjects will be recruited through a variety of online avenues and local autism community groups and organizations, as well as advertising to the general public.
- Project Rex is an autism-focused program directed by Dr. Gwynette at MUSC, and has a robust social media network, a website with significant traffic, and a large patient directory. Information regarding the study and digital copies of fliers will be posted on social media forums (Facebook, Twitter, Instagram) under existing Project Rex accounts, as well as sent via email to the Project Rex mailing directory. Dr. Gwynette may discuss the study with patients they are actively treating as well as their family members. The study may also be advertised at any other groups, projects, or events that are being run conducted Project Rex.
- In addition to Project Rex, investigators will reach out to other local autism organizations and groups such as the Lowcountry Autism Foundation (LAF), the Lowcountry Autism Consortium, South Carolina Autism Society to provide information regarding the study to their members, as well as digital and/or physical copies of fliers to distribute to their members if they are willing to do so. Investigators will also offer to come to speak about the study and answer questions during group meetings in person for any groups who are interested. Emails will be distributed by the investigators to families and stakeholders on the Project Rex newsletter distribution list and the MUSC broadcast email system.
- Flyers will also be posted around the MUSC campus and hospital once approved.
- Investigators will reach out to local psychiatry offices and provide them with information regarding the study and digital and/or physical copies of fliers for them to share with their patients at their discretion.

- Flyers will be given to the parents of children who are enrolled in PEERS. Flyers and posters will contain information including a basic explanation of the study (investigating the use of non-invasive brain stimulation for enhancement of learning social skills in autism), eligibility (age range, diagnosis of ASD), information about financial compensation and ability to receive behavioral intervention at no cost to patient. They will also include study site and contact information for study coordinator(s).

9.0 Consent Process

Consent will take place at the Center for Biomedical Imaging at 30 Bee St on the campus of MUSC. The research coordinator will explain study procedures to the parent (or authorized legal guardian) and adolescent with ASD. Pictorial descriptions will be provided along with verbal descriptions, which is a well-accepted practice when describing research study procedures to individuals with ASD. During the consent process, the investigator will make clear that different activities will be completed by the parent and the child. To assess level of interest from youth with ASD, the coordinator will ask the parent or child volunteer if he or she has any questions about the study procedures. Following this, the coordinator will directly ask the child if he or she wants to participate. A verbal indication of "yes" or nodding of the head will be taken as assent. The child will be asked to provide their signature on an assent form. Parents will provide written consent. If either the child or parent fails to provide assent or consent, the child will not participate and will not be enrolled in the study. The parent will provide written consent for their participation. There will be no waiting period between informing the prospective subject and obtaining the consent.

The oldest adolescent participants will be 17 years of age upon enrollment. If a volunteer turns 18 during the course of the study, they will be reconsented as an adult at the next visit following their 18th birthday. Decision capacity will not need to be determined at this point because all participants will have scored in the normal range for IQ as part of the inclusion criteria.

During the study, continued assent/consent from the ASD volunteers will be indicated by willingness to participate in the PEERS group intervention , willingness to wear the tDCS electrodes, and willingness to enter the MRI scanner. Verbal or non-verbal protests for any of these procedures will indicate unwillingness to participate. However, additional attempts will be made to encourage participation within the same session. If the child continues to protest or becomes agitated, uncomfortable or non-responsive to experimenter instructions, the procedures will not be continued for that session. The child is encouraged to return for additional sessions, but will not be forced to do so.

10.0 Study Design / Methods

We will conduct brain stimulation with 17 randomized adolescent participants at initial enrollment. Drop-outs are expected, with the goal of having 10 youths with ASD complete the study, with the same number of parents actively participating by the end of the experiment.

The following table summarizes the schedule of activities for a subject:

Schedule of events	Activities	Time commitment for volunteer	Compensation
Initial visit with research coordinator, Drs. Gwynette and Carpenter	Consent (parent and child)	15 min	$25 (child) $15 (parent)
	Medical & MRI screening (parent and child)	5 min	
	ADOS-2 & KBIT-2 (with child), clinical measures (with parent)	90 min	

	Mock scanner training with child	10-15 min	
	fMRI scanning with child	30 min	
	tDCS acclimation with child	10 min	
PEERS weekly sessions	PEERS training plus active / sham tDCS	1 hr / week x 14 weeks	$15 per session (child) $0 (parent)
Post-intervention visit	clinical measures (with parent), fMRI scanning (with child)	45 minutes	$25 (child) $25 (parent)
14-week follow-up visit	clinical measures completed online (by parent)	30 minutes	$10 (child) $50 (parent)

Parents will make initial phone or email contact with the study coordinator. The study coordinator will conduct a brief telephone screening to determine preliminary eligibility for the study. If eligible, the study coordinator will schedule the initial visit.

The initial visit will last approximately 3 hours. Following informed consent (see Section 9.0), an in-depth MRI screening form will be filled out by the parent and the medical history information obtained during the initial telephone interview will be reconfirmed. Any female participants will complete a pregnancy test. Dr. Carpenter will then conduct the ADOS and K-BIT with the child while the parent completes the following clinical outcome measures on a computer (using RedCap) in a separate room: Social Responsiveness Scale-2 [26], the Social Skills Improvement System, the Quality of Play Questionnaire, the Aberrant Behavior Checklist, and the Test of Adolescent Social Skills Knowledge-Revised [27]. The child and parent are given a 10-minute break and a healthy snack, if desired.

Following the break, the child is introduced to the tDCS electrodes placed on the scalp with no stimulation as an initial step in the acclimation process. Because some individuals with ASD can be excessively sensitive to certain sensory stimuli, this initial introduction to the electrodes is important. While the subject is being acclimated to the electrodes, the research coordinator explains the fMRI task to the child and demonstrates the task on a computer. The electrodes are removed, then the child is placed in the mock scanner. The mock scanner introduces the participants to the scanning environment by laying in the bore of a simulated scanner, listening to MRI sounds, practicing button presses and playing a game that awards points for keeping head movement to a minimum (via a head tracker in the mock scanner controlling the cursor – the longer the subject keeps their head in the same location, the longer the cursor stays on a bullseye and the more points they accumulate). Participants will play the bullseye game for 5 minutes. Dr. Joseph's prior experience in scanning youths with ASD indicates that they can keep their heads still for this period of time. The subject will then practice the fMRI task in the mock scanner for about 3 minutes.

After mock scanner training, subjects are taken to the MRI scanner and placed on the scanner bed in a comfortable position, with blankets and head cushioning. The child is told that the parent is always nearby and that the research team will be able to talk to them through the headphones. Additional ear protection is provided in the form of foam ear plugs. When subjects are in the scanner but not performing any particular task, a movie will be played for them. The child is given a button box to hold in their dominant hand in order to make responses during the fMRI task. In the other hand is a squeeze ball that should only be used to alert the research team if they feel panicked and need to come out of the scanner. During scanning, the research coordinator and MRI technician are in frequent verbal contact with the subject and will always tell the subject what to expect in terms of noises and duration of a scan. Total scanning time is approximately 20 minutes.

Pre- and post-treatment fMRI sessions will use a task in which two visual stimuli are presented simultaneously then removed, with the location of one image replaced by a probe[28]. Participants respond with the index or middle finger of the preferred hand to indicate the probe location. In this type of probe task, brain activation is expected to be higher for probes that are in the same location as the stimulus that is attended more. Reaction time is also expected to be faster if the probe appears in a location that was just recently attended compared to the location that was not attended. In one condition, the stimuli are a face and house to assess attentional bias to faces versus non-faces (related to social awareness). Another condition presents a face with direct gaze and one with averted gaze (related to social motivation, social anxiety). These conditions are implemented in functional runs lasting 5 minutes each and each run is repeated twice. The runs are presented in counterbalanced order across subjects. Following fMRI scanning, an additional tDCS acclimation session is completed. Electrodes are placed on the scalp again, and current is gradually increased to the desired level over a 5-minute period. The child will watch a movie or play a video game during this acclimation period.

Following the baseline visit, subjects will return on a different day for the PEERS training. PEERS is a parent-assisted intervention that teaches targeted social skills to high-functioning patients with ASD during fourteen weekly sessions. Parents and adolescents attend separate concurrent sessions that instruct them on key elements about making and keeping friends.

Each adolescent PEERS session begins with a didactic section, approximately 30 minutes in duration. Then the group conducts role plays modeling the correct and incorrect ways to utilize the weekly skill set. Next, the group reviews homework from last week and then discusses homework for next week. During the last 10-15 minutes of the session, the adolescents and parents are reunified to discuss the homework assigned for next week.

Each parent session begins with a detailed review of each adolescent's progress on the previous week's homework. Then the parents are given didactic information about the weekly skills set. Finally, the parents are reunified with the adolescents in order to discuss the plan for completion of assigned homework for next week.

Topics covered during the PEERS program include the following:

1. Conversational skills, including verbal and nonverbal forms of communication;
2. Electronic forms of communication, including phone calls, text messaging, instant messaging, emailing, and online safety;
3. Developing friendship networks, including identifying relevant peer
4. Groups and extra-curricular activities in which to find sources of potential friends;
5. Appropriate use of humor, including learning to pay attention to humor feedback from others;
6. Peer entry strategies, including how to join conversations with other adolescents;
7. Peer exiting strategies, including how to assess receptiveness during peer entry and what to do when these attempts fail;
8. How to have successful get-togethers, including how to organize and execute a gathering with friends;
9. Good sportsmanship, including how to appropriately behave during games and sports;
10. Handling teasing, including distinguishing teasing from embarrassing feedback and handling verbal teasing through the use of appropriate behavioral responses;
11. Handling bullying, including identifying strategies for handling cyber bullying and physical threats from others;
12. Changing reputations, including long-term strategies for altering a bad reputation;
13. Resolving arguments with friends, including specific steps for problem solving disagreements; and handling rumors and gossip, including behavioral strategies for minimizing the damage caused by gossip.

Subjects will receive tDCS weekly in conjunction withtheir PEERS session. Half of the adolescent participants will be randomly assigned to receive active tDCS of the left dorsolateral prefrontal cortex (DLPFC), and half will receive sham tDCS to the same location. Active / sham assignment does not change over the course of the experiment. However, within each condition, half of the participants will receive tDCS during the first 30 minutes and half will receive tDCS during the second 30 minutes. This schedule will then be reversed at each session. This will counterbalance the time of tDCS delivery and will increase the feasibility of setting up tDCS in a reasonable time window. Sham tDCS is achieved by wiring all group participants to separate computer-controlled tDCS programs. All participants receive an initial brief dose; those receiving sham treatment are then automatically decreased to zero by the computer, allowing all clinical personnel to remain blind to the participant's condition. Participants themselves are also blind to condition as most people report that the tingling sensation associated with tDCS decreases within the first few minutes of treatment.

For participants randomized to receive active treatment, tDCS will be delivered in 30-minute sessions with the Chattanooga Ionto system using 1.5mA current. This constant current device ramps up to the desired amplitude to minimize discomfort for participants and ramps the amplitude back to 0mA at the end of the session. Electrodes will be standard small (4x4 cm) sponge electrodes soaked in a sterile solution of 0.9% sodium chloride insulated by a latex casing. The current density and total charge delivered by the above parameters is consistent with those used safely in the current research literature. In all tDCS conditions, the anode will be placed on the scalp over the area corresponding to the left DLPFC (position F3 from the EEG 10-20 system located via a commercial EEG electrode placement cap), a brain region postulated to have deficient neural inhibition in ASD [29-30] and demonstrated to be a potential tDCS site for the reduction of symptoms associated with ASD[21]. The cathode will be on the scalp over the area corresponding to the right DLPFC (position F4 from the EEG 10-20 system located via a commercial EEG electrode placement cap). Specially designed software (authored by investigator Borckardt) interfaces with an ONTRAK ADU218 Solid State Relay I/O interface connected to the tDCS device permitting normal and reverse current flow between the electrodes in a manner that is completely masked. The software reads the assigned condition directly from an encrypted participant-randomization-file and delivers anodal or sham stimulation in a blinded fashion.

A brief questionnaire about adverse effects will be completed with participants and their parents immediately following the second and last treatment sessions. Tolerance for tDCS will be monitored during tDCS delivery by noting the frequency with which a subject reported irritation, discomfort, burning or pain, whether a subject attempted to remove the tDCS leads, whether a subject wished to discontinue the procedures due to the tDCS (rather than the PEERS training). After the second and last PEERS sessions, the experimenters will administer a brief questionnaire with the subject about whether they felt uncomfortable itching, tingling, burning during the session or whether they have had headaches, neck pain, sleepiness, moodiness in the past week. Any of these effects will be recorded. We will conclude that tDCS can be tolerated if these effects are experienced less than 25% of the time for a given individual. We will also report on how many subjects tolerated the procedures.

The child and parent receive compensation in the form of gift cards following each visit to MUSC (see Table above).

After 14-weeks of PEERS training, subjects will return for a post-treatment session in which the clinical outcome measures will be completed by parents and fMRI session will be completed by the participants (same procedures as before excluding tDCS acclimation).

Finally, 14 weeks after the post-treatment session, the parent will be sent a reminder via RedCap to complete the clinical outcome measures. In addition, both parent and child will be asked to guess which condition the child was assigned to (active or sham tDCS). Once the final follow-up surveys are completed in RedCap, the final gift card of $75 is mailed to the family.

Information about which condition a subject was assigned to is not typically provided, but if a subject asks, we can tell them after all study procedures are completed and the blind is lifted. Study personnel will also be asked to guess the condition before the study blind is lifted.

Source records: the data collected from subjects include: parental and subject responses on clinical tests and questionnaires, anatomical and functional MRI scans, reaction time and accuracy responses on the fMRI task.

11.0 Specimen Collection and Banking (if applicable)

N/A

12.0 Data Management

Statistical Power. Schneider and Hopp [4] reported an effect size of 2.87 (Cohen's d) for improvement in syntax acquisition in minimally verbal children with autism following 30 minutes of tDCS. This large effect size requires a minimum sample size of 10 subjects, which is comparable to the proposed sample size. However, that studied tested a different domain (syntax acquisition) from the present study (social cognition and communication) and sample of children with higher autism severity. Nevertheless, those initial findings are promising indicators of the efficacy of the use of tDCS in ASD.

Data Analysis plan.

- **AIM 1**: We predict that adverse effects and ratings of discomfort, pain, and side effects will be minimal. Only descriptive statistics will be used – frequency of reports of different types of discomfort or pain.

- **AIM 2**: We predict that participants receiving active tDCS will show greater improvement on the Social Responsiveness Scale, the Social Skills Improvement System, the Quality of Play Questionnaire, the Aberrant Behavior Checklist, and the Test of Adolescent Social Skills Knowledge-Revised compared to those receiving sham tDCS. This will be assessed by examining descriptive statistics for each measure..

- **AIM 3**: We predict that after intervention, all participants will show increased social brain network response to faces (v. objects) and to direct (v. averted gaze), with a greater response in those receiving active tDCS. The analysis of fMRI data will include preprocessing (geometric distortion correction, head motion and slice timing correction, spatial (7-mm FWHM) and temporal high-pass (100 sec cutoff) filtering and spatial normalization to MNI space via each subject's high-resolution T1 MPRAGE image. Eight regions of interest (ROIs) will be defined as 10-mm diameter spheres located in left and right medial prefrontal cortex, left and right temporoparietal junction, left and right fusiform gyrus, left and right amygdala, based on prior studies of face processing. In each ROI, percent signal change for faces v. objects or for direct v. averted gaze will be extracted for each subject and for each time point. The effect of tDCS on fMRI signal will be assessed with descriptive statistics.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This project involves both a medical device intervention (tDCS) and a behavioral intervention (PEERS training). fMRI scanning, while not an intervention, will be conducted prior to and following 14-weeks of weekly tDCS sessions.

For tDCS, safety of the participants will be monitored during and immediately after delivery of tDCS to the scalp. During tDCS stimulation, subjects have the option of wearing a ski cap which may reduce discomfort. They will be introduced to the ski cap during the tDCS acclimation session on the initial visit. Some subjects may opt not to wear the ski cap, but it will not affect tDCS delivery. At the end of the sessions that involved tDCS delivery, subjects will be asked if they felt or feel any sensations on the scalp where the electrode was and responses are recorded by the experimenter. In Dr. Borckardt's experience and other reports in the literature, any sensations of pain, tingling, itching, stinging or irritation follow the onset of stimulation for about 30-60 seconds and do not persist longer than that. If subjects report feelings of sensation or pain that are unmanageable, a local analgesic cream (benzocaine) can be used or the level of current can be reduced to help them complete the session. Dr. Gwynette will be present during all experimental sessions when tDCS is delivered and will be able to monitor for any adverse medical effects.

Adverse effects will be defined by painful sensations that are unmanageable and cannot be alleviated using the procedures outlined above or by persistent reports of high levels of pain by a participant. Although we do not expect this to occur, such events will be reported to the IRB.

For PEERS training, which is a behavioral intervention, the risks are minimal, but include potential discomfort in interacting with other individuals. Should this intervention prove to be too distressful for an individual, the individual will have the option to discontinue the study. Distress would be indicated by persistent withdrawal from or refusal to engage in PEERS activity, persistent protesting, crying or agitation during PEERS sessions. Dr. Gwynette and the research assistant will make the decision as to whether an individual is experiencing distress. When these behaviors lead to removal from the study, these will be reported as adverse events to the IRB.

To protect against risks associated with fMRI scanning, the following procedures are followed. To minimize discomfort in the MRI scanner, every attempt will be made to maximize the comfort of the participant by using pillows or other supportive materials for neck and back support and by keeping the time in the scanner to a minimum, without sacrificing quality of experimental design. To prevent eye strain and dry eyes, we will suggest that volunteers use eye drops before the experiment, if necessary.
To protect against the loud noise of the MRI scanner, all participants are required to wear ear protection provided by the experimenter. Some participants could experience claustrophobia. To prevent this, one of the screening questions on the telephone questionnaire asks about a history of claustrophobia. However, some individuals may not know they are claustrophobic. One measure to screen for this is the use of mock scanner prior to the real scanning session. This allows some individuals to figure out whether they would not tolerate the enclosed space before entering the real MRI scanner. However, if an individual experiences panic or anxiety at any point while in the MRI scanner, he or she is removed immediately from the scanner. While in the MRI scanner, the volunteer holds a squeeze ball that produces a loud noise in the control room that can be heard over the noise of the scanner and stops the scanner. The experimenters will query the volunteer immediately upon hearing the squeeze ball to determine whether the subject is experiening any kind of panic or anxiety. If so, the subject is removed from the scanner immediately and allowed to rest comfortably in a chair outside of the scanner area until he or she feels calmer. The participant is invited to re-enter the scanner at another time, if they wish. To prevent dizziness from moving too quickly within the magnetic field, individuals are instructed to move slowly when laying down and sitting up from the MRI scanner bed. The scanner bed moves very slowly to avoid this reaction. To minimize the chance for injury due to the presence of metal in the body (excluding dental fillings and permanent retainers) and surgical implants, several measures are taken. First, the telephone interview asks about the presence of metal or devices in the body as well as any conditions that might have put the individual at risk for having metal in the body (e.g. welding and

combat). Second, upon arrival for the study, the individual signs a checklist ensuring that no metal is in the body. Third, a small metal detector is also used at this time to make sure that the subject has removed all metal (jewelry, coins, belts, hair accessories) from the body. If there is any chance that metal exists in the subject's body (e.g., a history or welding without eye protection or piercings) that cannot be removed for purposes of the experiment, the individual is not allowed to enter the MRI scanner. There is no risk for injury to the subject or risk for damage to the equipment if all metal has been removed from the body and no metal exists in the body. The screening procedures make every attempt to isolate all conditions that could potentially lead to injury. However, if the individual does not respond truthfully to these inquiries (or may have forgotten some condition), we will have no way to know that metal is present in the body. Consequently, there is a potential risk for injury in this case.

High-resolution anatomical scans collected for research purposes as part of the study could reveal some type of brain abnormality or pathology. The consent form states that the scanning sequences are not optimized to detect clinical conditions and that the MRI scans will not undergo routine reading by a qualified neuroradiologist. However, if the research investigators notice something unusual in the MRI images, Dr. Leo Bonilha will be consulted to detemine whether the incidental finding requires an urgent response. If Dr. Bonilha deems that the finding is urgent or if the parent and volunteer should be notified, the PI will contact the volunteer and parent. If the volunteer/parent would like the brain images collected as part of this study to share with their physician, we will provide a copy of the images directly to the volunteer.

Response to adverse events for fMRI: Although the risks of MRI scanning are fairly minimal if all safety precautions and subject screenings are followed, very rarely adverse events could occur. For example, in the presence of a strong magnetic field metal objects can be sucked into the scanner and become projectiles causing injury to the subject or personnel. Other potential adverse events (which are very rare) might include injuries at the scanner (due to undetected or unreported metal in the body heating up or moving in the magnetic field) or intense panic reactions that might need medical attention. The CBI requires that two study personnel (or an MRI-technologist and an individual from the research team) must be present while scanning a subject. In the rare case that a subject requires medical attention at the scanner during an experiment, one of the experimenters or technologist will immediately dial 911 (the research MRI scanner at 30 Bee St is not part of the hospital system so we need to dial 911 for emergencies). The other experimenter will attend to the subject by safely removing him / her from the scanner and placing him or her on the MRI-compatible patient bed (with the help of the second experimenter once a call for help is made).

Confidentiality is achieved by (1) assigning a random code to each subject to de-identify data collected from the subject and storing that data with the code rather than with any personal identifiers, (2) storing any personal identifying information in locked files cabinets in Clinical Sciences Building Room 325F, (3) only allowing study personnel to be present at the MRI scanner at 30 Bee Street during the experiment, (4) training study personnel to never refer to individual participants by name (or to their parents by name), and (5) never identifying an individual participant in scientific papers that summarize the results of the studies.

The de-identified electronic data associated with individual subjects will be stored on MUSC secure hard drives accessible only to study personnel. A master file that links a subject's identity to the random code will also be saved on MUSC secure hard drives in a password protected file.

14.0 Withdrawal of Subjects (if applicable)

Subjects can withdraw from the study voluntarily. Although financial incentives will be provided for continued participation, subjects are not forced or otherwise coerced to participate.

The investigators may withdraw an individual from the study for the following reasons: (a) participant does not understand or follow instructions, (b) participant is not cooperative or is disruptive during PEERS/ tDCS delivery or fMRI scanning sessions, (c) the safety of the individual is at risk due to tDCS

delivery, as described above (persistent or intense experience of pain), (d) the subject exhibits severe psychological distress or anxiety during tDCS delivery, PEERS activities or fMRI scanning. If any of these reasons leads to withdrawal from the study, Drs. Gwynette / Joseph would discuss the reason(s) with the child and parent as soon as possible following the incident. This could be immediate if only the volunteer would be affected (e.g., during fMRI scanning), but if there are disruptions or a failure to follow instructions during a PEERS session (which takes place in a group format), Dr. Gwynette will discuss the issue with the parents following the session.

15.0 Risks to Subjects

The risks to the adolescent subjects are as follows:

Participants may feel restless or uncomfortable when lying in the MRI scanner. This may occur and is generally not serious.

Eye strain and dry eyes may occur. This occurs occasionally but is not serious

The MRI scanner produces loud noise. With adequate ear protection provided by the experimenters, this is not a significant risk.

Some participants could experience claustrophobia. This occurs infrequently.

Moving too quickly within the magnetic field can cause dizziness. This occurs occasionally but is not serious.

The presence of metal in the body (excluding dental fillings or some types of permanent retainers) and surgical implants can potentially cause injury when the individual is placed in a strong magnetic field. This occurs very rarely if subjects are well-screened. It is serious.

High-resolution anatomical scans collected for research purposes as part of the study could reveal some type of brain abnormality or pathology. This occurs very rarely and may be serious.

tDCS has been linked to onset of seizures in people with epilepsy, but the likelihood of inducing seizures in people without epilepsy is extremely low.

tDCS may cause itching, tingling, burning and discomfort at the site of delivery on the scalp. Headaches have also been reported.

Some of the activities during PEERS training (e.g., role-playing) may cause mild self-consciousness or embarrassment for some individuals. There is potential loss of privacy due to participating in group discussions.

There is potential loss of confidentiality of research records.

The risks to the parents are as follows:

There is potential loss of confidentiality of research records.

16.0 Potential Benefits to Subjects or Others

The potential benefit of this study is that tDCS and/or PEERS training will improve social interaction and communication skills in individuals with ASD.

This could also have secondary benefits for family members and friends of the research participants.

This study involves procedures for which the risks are known to be minimal; therefore, the potential benefit of improved social communication and interaction outweighs these risks.

17.0 Sharing of Results with Subjects

Parents will be provided with a brief written summary of ADOS and Cognitive results upon request. As discussed above in Section 13.0, incidental findings will be shared with the parent. Disclosure of the random assignment of active versus sham tDCS will be provided upon request.

18.0 Drugs or Devices (if applicable)

The tDCS devices, accessories and laptops used in this study will be stored in the Institute of Psychiatry South, 5th floor in a locked cabinet. Only authorized personnel have access to the devices. The research coordinator will be trained in the use and proper storage of the devices.

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