INTERVENTIONAL RESEARCH PROTOCOL

(HRP-503a)

STUDY INFORMATION

- **Title of Project**: A Pilot Study of Transcranial Direct Current Stimulation in Children with ASD

- **Principal Investigator**
  Barbie Zimmerman-Bier M.D.
  Clinical Associate Professor

- **Principal Investigator Div. & Dept.**
  Department of Pediatrics, Division of Pediatric Neurology Robert Wood Johnson Medical School (RWJMS)

- **Principal Investigator Contact Info:**
  Children's Health Institute 89 French Street, RM 1218 New Brunswick NJ 08901
  Telephone Number 732-235-7083
  zimmerba@rwjms.rutgers.edu

- **Protocol Version and Date: v1 1/ 17/2021**

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

	TOPIC	PAGE
1.0	Research Design	**3**
1.1	Purpose/Specific Aims	4
1.2	Research Significance	4
	Research Design and Methods	5-11
1.4	Preliminary Data	11-12
1.5	Sample Size Justification	12
1.6	Study Variables	12-13
1.7	Drugs/Devices/Biologics	13
1.8	Specimen Collection	13
1.9	Data Collection	13-14
1.10	Timetable/Schedule of Events	14-15
2.0	Project Management	
2.1	Research Staff and Qualifications	14-15
2.2	Research Staff Training	15
2.3	Resources Available	15-16
2.4	Research Sites	16-17
3.0	Multi-Center Research	
4.0	Subject Considerations	
4.1	Subject Selection and Enrollment Considerations	18-19
4.2	Secondary Subjects	19
4.3	Number of Subjects	19
4.4	Consent Procedures	19-21
4.5	Special Consent Populations	21
4.6	Economic Burden and/or Compensation For Subjects	21
4.7	Risks of Harm/Potential for Benefits to Subjects to Subjects	22-23
5.0	Special Considerations	
5.1	Health Insurance Portability and Accountability Act (HIPAA)	23
5.2	Family Educational Rights and Privacy Act (FERPA)	23
5.3	Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)	23
5.4	General Data Protection Regulation (GDPR)	23
5.5	NJ Access to Medical Research Act (Surrogate Consent)	23
6.0	Data Management Plan	
6.1	Data Analysis	24-
6.2	Data Security	25
6.3	Data Safety And Monitoring	26-27
6.4	Reporting Results	27-28
6.5	Secondary Use of the Data	28
7.0	Research Repositories – Specimens and/or Data	28
8.0	Approvals/Authorizations	28
9.0	Bibliography	28-32

1.0 Research Design

1.1 Purpose/Specific Aims

A. Objectives

Although many children diagnosed with ASD make significant progress in learning and their cognitive skills improve with applied behavior analysis (ABA) and other teaching techniques, there are a significant number who show an absence or a plateau in various skills. Deficits in executive functioning are likely to be involved in many of these cognitive and learning disabilities due to poor functioning of the prefrontal cortex. Currently, the use of biological methods for improving learning and cognition is largely unexplored in research and practice.
Transcranial Direct Current Stimulation (tDCS) is a low-level electrical neurostimulation that has been used for various indications for decades and with no serious side effects. There is accumulating evidence that tDCS is effective in treating the comorbidities as well as the core symptoms of ASD. tDCS is most effective when used simultaneously with an active intervention. In this study, we will extract the effects of tDCS alone and in combination with ABA on the executive functioning skills and the core symptoms of ASD and monitor the results using an objective neurophysiological test (EEG).

The objective of this study is to pilot the use of transcranial direct current stimulation (tDCS) in combination with behavioral intervention to improve the acquisition of educational programs for students with ASD.

We will be working with students in structured programs that provide comprehensive applied behavior analysis (ABA) with objective interventions and employ data-based evidence to guide the educational programs, either in-school or in-home. **tDCS has been used for various indications over a couple of decades and has been shown to be very safe (30,000 treatment episodes yielded no serious side effects) and has been well-tolerated by children with ASD.** The mechanism of tDCS's effectiveness is not clear, however animal studies show that tDCS can stimulate the flow of calcium ions through channels in the astrocytes, activating them, and facilitating their role in synapse formation and therefore learning.

B. Hypotheses / Research Question(s)

Aim #1: To pilot the use of tDCS to children with ASD enrolled in ABA programs. We intend to provide the stimulation during the ABA therapy sessions focused on preselected cognitive programs and measure the outcome via a standardized instrument, and we will also use discrete acquisition data compiled as part of the students programming.

There is accumulation evidence that tDCS is effective in treating the core symptoms of ASD as well as co-morbidities, but there are still gaps in our knowledge. Nearly all the existing studies were done on high functioning adults with ASD. The larger double-blind studies utilized general ASD outcome measures and specific comorbid symptoms were not examined, especially in combination with evidence-based intervention in a natural environment setting. This research study further our understanding of the benefits of tDCS in treating the comorbidities and core symptoms in children with ASD.

Aim #2: To evaluate a biomarker of brain complexity at various points (before, during, and after the treatment) obtained through EEG measurements. We will use portable EEG devices which can be used in the therapy session. We hypothesize that through this treatment, circuits will be made more functional and this will be associated with increased complexity measured on the EEG, which has been shown to be associated with typical functioning when compared to ASD brainwaves.

EEG data will be obtained and analyzed for complexity with a unique algorithm previously successful in separating ASD from controls and predicting outcome in children as young as 3 months old (Bosl, Tierney et al., 2011; Bosl, Tager-Flusberg et al., 2018). The question of whether this will be predictive (at baseline) or associated with clinical improvement will be investigated.

1.2 Research Significance

ASD is a highly heterogeneous disorder with numerous presentations, etiologies, and pathophysiology (London, 2014; Waterhouse, London et al., 2017). When devising treatments for ASD, the heterogeneity makes any unified biologic etiology or pathophysiology highly unlikely. Although many children diagnosed with ASD make significant progress in learning and their cognitive skills improve with ABA, there are many who show an absence or a plateau in various skills (Eaves & Ho 2008; Fein, Barton et al., 2013). It is more likely that the treatment for ASD will have to be a hybrid of the medical and behavioral models. There have been numerous calls for combining the two models of treatment, however for various reasons there is scant research on combined treatment (Yoo, Williams et al., 2003; Zarcone, Lindauer et al., 2004; Weeden, Ehrhardt et al., 2009). **This proposal uses a novel biologic intervention that combines electrical brain stimulation with ABA treatment to target some of the cognitive deficits in ASD that until now have been relatively refractory to treatment.**

There has been a growing enthusiasm for electrical stimulation techniques in all fields of treatment for brain disorders of various types. Noninvasive brain stimulation methods include transcranial magnetic stimulation (TMS), **transcranial direct current stimulation (tDCS),** transcranial alternating current stimulation, high frequency random noise therapy, transcutaneous vagal stimulation, transcutaneous trigeminal stimulation and others (Paulus, 2011). The two most studied and promising for ASD are tDCS and TMS. Although TMS has shown success in ASD (Casanova, Hensley et al., 2014; Sokhadze, Casanova et al., 2017), a recent consensus statement emphasizes the need for better designed studies before this could be recommended as am indicated clinical treatment for autism (Cole, Enticott et al., 2019).

We have chosen to study tDCS for several reasons.

1. As explained above there is reason to believe that brain stimulation in combination with training or rehabilitation will yield maximal results (Page, Cunningham et al. 2015; Sathappan, Luber et al., 2019).
2. Both modalities can be combined with intervention, however tDCS is easily portable and so can be used in the locations in which teaching or training takes place, even at home.
3. It is also much less expensive and therefore could be widely used.
4. It is remarkably safe

tDCS delivers exceedingly small amounts of energy to the brain compared to other forms of stimulation. Other forms of stimulation create an action potential and therefore drive the circuits which are being stimulated, and do not depend on the training component for their effect. tDCS works in conjunction with the training component of therapy. In theory, tDCS works by stimulating the circuits that are being used or exercised by the training component. Due to inadequate neuromodulation (London, 2018), the circuits are not firing efficiently. The small currents generated, rather than making the cells fire, create an improved neuromodulation, making the cells more amenable to firing. In this way, tDCS enhances the effectiveness of behavioral therapy and causes more efficient neuromodulation.

Executive function deficits are common in children with ASD (Pennington & Ozonoff, 1996; Geurts et al., 2014). Given this deficit in executive functioning skills in people with ASD, several studies have examined the effects of tDCS on high functioning adults with ASD. Other studies have found reduction in the core symptoms of ASD in children **See preliminary data**

tDCS has used for a host of indications including pain management, ADHD, depression, cognitive

Study ID	Randomization Schedule	ARM 1	ARM 2
001	1	tDCS	Sham

improvement, language improvement, stroke rehabilitation, OCD and many more. The length of treatment is typically 20 minutes. There is still much debate, as to the frequency of treatment. Many studies have used single treatment episodes while others have treated for longer intervals such as a week or a month once or twice per day. We have chosen to treat for 20 sessions over 4 weeks which is the protocol used in one of the two controlled randomized crossover studies done in ASD on 24 participants (the largest to date) (Gómez, Vidal et al., 2017). **The safety of tDCS is remarkable, compared to nearly any other biologic treatments which have been used. In a review of over 30,000 treatment episodes, there were no serious side effect noted** (Bikson, Grossman et al., 2016). Safety in children has also been addressed and similar to adults, the most common side effect is a tingling feeling under the electrode (which is short lived) in about 10% of children. About 5% of children report some temporary itching or reddening under the electrode and, again, no serious side effects (Krishnan, Santos et al., 2015).

In addition, we will be piloting the use of EEG prior to treatment as a digital biomarker which could predict response to the tDCS, and we will get EEGs before and after each arm of treatment/. We will be using an algorithm which measures EEG complexity and this method has been shown to be highly predictive of ASD from non-ASD in children as early as 3 months of age (Bosl, Tager-Flusberg et al., 2018). See preliminary data.

1.3 Research Design and Methods

A. Research Procedures

- **Study Subjects**

Participants will include school-aged children with ASD between the ages 5-12. We selected this age group because a diagnosis is typically made by the age of 5. This age group also allows us to profit from neuroplasticity while avoiding potential variables related to children undergoing puberty. This age group is also likely to be enrolled in intensive ABA programs aimed at executive functioning and social communication intervention. Based on the gender distribution of ASD in the population, we expect that our group will be approximately 75% male. Participants will be recruited from the local New Jersey community, from ABA schools and ABA agencies.

- **Experimental Design**

The study will use a randomized double-blind controlled placebo (sham tDCS) crossover design. The study will involve 5 total months of participation. Participants will be randomized into two groups using a random number generator. They will receive either:

A) 20 active tDCS stimulation followed by 20 sham stimulation: or
B) 20 sham stimulation followed by 20 active tDCS stimulation.

- **Randomization & Blinding**

We anticipate recruiting 24 participants in anticipation of 4 subjects dropping out. We will use SAS programming to generate a randomization schedule with a block length of 6 and four blocks. Participants will enter the randomization schedule after consent is obtained and they are assigned a study ID.

002	2	Sham	tDCS
003	2	Sham	tDCS
004	1	tDCS	Sham
005	2	Sham	tDCS
006	1	tDCS	Sham

Block 1 example- there will be four blocks = 24 participants recruited.

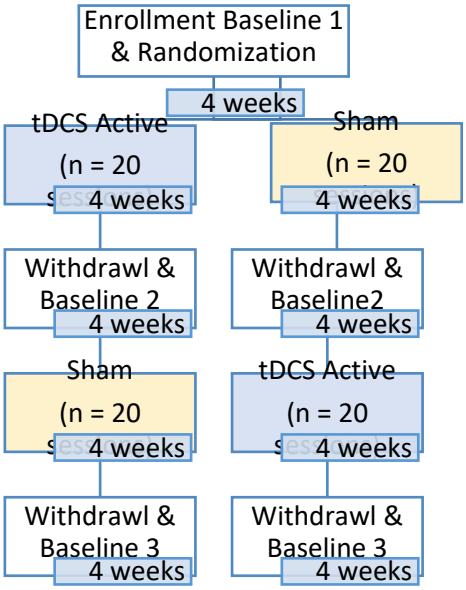
Subjects 21-24 (to account for drop outs) will receive randomization order of the subject they are replacing but will receive a new study ID. For example if the subject with study ID 004 drops out then subject with study ID0021 will receive randomization schedule 1.

Dr. Yoo will utilize the generated randomization schedule to provide active tDCS and sham stimulation codes that will be entered into the tDCS device (by the parent) prior to each session. These numeric codes will be random numbers and not distinct to the study group assignment, protecting the blind. Because of her role, Dr. Yoo will remain unblinded and will not be involved in any assessments. All other study staff, including Drs. Zimmerman-Bier, London, and Bosl, will remain blind. Parents, participants, and ABA providers will also remain blind.

Both active and sham stimulations will be implemented once per weekday while children receive their regularly scheduled in-home or school-based ABA. Participants will be asked to continue their routine medication and behavioral regimen throughout the duration of the 5-month study. Participant's parent or caregiver will be trained to use the tDCS device. They will be trained on how to turn on the device and enter the active or sham codes, as well as how to place the headgear in place. Our previous parent trainings typically took less than 30-mins and parents found them easy to use. If no parent or caregiver is available or willing during ABA therapy to apply the tDCS, a research assistant will travel to the participant's ABA session to conduct the study sessions.

- Enrollment Baseline 1 (Assessment) Randomization and Desensitization = 4-week
- 4 week/20 sessions of 1mA active or sham tDCS stimulation (depending on order assignment)
- 4-week washout, then assessment
- 4 week/ 20 sessions of 1mA active or sham tDCS stimulation (depending on order assignment)
- 4-week washout, then assessment
- Discuss with study PI about open label – open label- up to 3 months

TABLE 1: Research Procedure



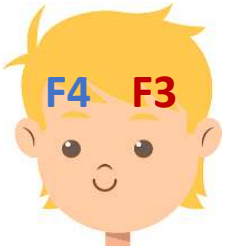
❖ **Device & Materials**

tDCS Device:

The Soterix Medical 1x1 mini-CT Stimulator Model 1601 will be used. The constant current stimulator will have a maximum output of 1.0mA.

Headgear: Each participant's head will be measured and fitted with a custom headgear (Soterix Medical SNAP headgear) to position the electrodes at designated tDCS montage (F3-F4) as accurately as possible.

Montage



The anodal electrode will be placed over F3 using the international 10–20 EEG electrode placement system to target the left dorsolateral prefrontal cortex (DLPFC) and the cathode electrode will be placed on the right dorsolateral prefrontal cortex. Forty stimulation sessions will be completed (20 active, 20 sham), each lasting 20 minutes per session at 1.0mA.

Montage		Total Number of tDCS Sessions	Duration of Each tDCS Session	Intensity of tDCS
Anode	**Cathode**			
F3	F4	40	20 mins	1.0 mA (milliamps)

Sponges: tDCS will be applied using a pair of disposables (i.e., onetime use) sponges pre-soaked with saline (Soterix Medical SNAP Pads).
Once the participant is seated, the preparation time will take about 3 minutes to set up the tDCS device, snap the sponges onto the electrodes, and place the headgear on the participant. At the end of the 20-minute session, the device will turn itself off automatically. The device will also pause if the conductance is poor (e.g., when the participant removes the headgear) and resume once the conductance is adequate.

Each caregiver/parent will be trained on how to set up the device and place the headgear on their child. If no caregiver can be identified or a caregiver is unavailable, a research assistant set up and place the headgear on the subject.

.

Difference between active vs. sham tDCS

Our tDCS device is designed to allow for sham (masked/placebo) stimulation. The active tDCS and sham are procedurally identical. Participants in both conditions will have the initial tingling sensation, except in sham stimulation, the current will be discontinued after 30 seconds while the power indicator remains.

Study tDCS treatment

Once the participant is seated and engaged in ABA therapy, it will take approximately 3-minutes to enter the study code, snap the two sponges on the headgear, and place the headgear on the participant to begin the active or sham stimulation. At the end of the 20-minute session, the device will turn itself off automatically. The device will also pause if the conductance is poor (e.g., when the participant removes the headgear) and resume once the conductance is adequate.

.

EEG

Electroencephalogram (EEG): The research assistant or study personnel will obtain a resting state EEG (non- sleep) at the subjects home (or in ICD research room if preferred) . **The Zeto portable eeg (https://zeto-inc.com/)** is a wireless dry or semi dry electrode system that is FDA cleared for clinical use as well as research grade. It is designed for rapid application and adjusts to head sizes from 3 years to adults. It looks like a bicycle helmet, requires no goop, does not pull-on hair and can minimize motion artifacts. It is a stand-alone unit that includes its own integrated amplifiers, digitizers, and 19 sensors on the head at the International 10/20 System locations. One to two minutes of awake, non-task-oriented EEG data will be recorded each EEG session The Zeto system can be individualized to use high quality dry or semi-dry sensors depending on the sensory needs of the child. The semi dry system uses disposable sensors that are easily inserted into the headset. The headset can be wiped down with water and alcohol between users. It has been widely in the home for clinical monitoring during the CoVid19 pandemic.

Participating subjects will be seated with eyes open while a research assistant applies the EEG device. The procedure will attempt to limit the amount of head movement. Continuous EEG recordings will be taken with a standard 10-20 system of electrode placement using equipment from Zeto.inc as described above. At least 2 minutes of baseline activity will be recorded after sensor impedances have been checked for acceptable contact. Electroencephalogram recording (EEG) will be collected at baseline, after the treatment period, and four weeks after the treatment during both phases.

Potential Problems

Effects from sham/placebo: Research-quality tDCS equipment has a built-in sham function. This produces a very small current for a few seconds at the beginning of the treatment. This is meant to simulate the active treatment which is a brief tingling of the skin under the electrodes which is rapidly accommodated to. In an evaluation of sham stimulation for placebo-controlled trials (Palm et al., 2013) it was found that participants were not able to distinguish between active tDCS and sham using the same prefrontal leads we are using in this study. In a recent review (Fonteneauet

al., 2019), there was an in depth questioning of the possibilities of the sham used in tDCS. They found that the blind could be compromised by the reddening under the electrodes which sometimes occurs. This is less of a problem in our study in that children have lower skin impedance and will have less reddening. In our preliminary work with children, we did not observe any reddening although this remains a possibility. A second issue is that in some studies, there has been a measurable effect even with this very small current for short durations however other studies have not found these effects.

Desensitization to tDCS headband: Children with ASD may not tolerate wearing the tDCS headband for 20 minutes while engaged in ABA therapy. In order to facilitate tolerance and cooperation, we will provide 2-3 desensitization sessions per day during a week-long period. An eligible participant must be able to wear the headset for the full 20 minutes during the last two desensitization sessions in order to enroll in the study.

Removal of tDCS headband: Despite these desensitization efforts, in a population of children with ASD, it is possible that participants may remove the tDCS headband during stimulation. This has occurred during our preliminary work, especially at 1.5mA (note that we are proposing to use 1.0mA in this study). The tDCS device however can immediately sense the change in impedance and turn itself off automatically. We were able to reinstitute the treatment in a relatively short amount of time (<1 min) and the participant received the full length of treatment. It is unlikely that a short interruption would change the effects of the treatment.

Non-consecutive sessions: We are proposing to stimulate participants during their weekday ABA sessions. It is possible that for a portion of the participants, completing 5-consecutive tDCS sessions during their ABA therapy may not be possible due to participant and/or therapist absence (holidays, illness, etc.). In such cases, we will make up those missed stimulation sessions in order to administer the total number of active and sham tDCS.

Research Timeline –

Please note that the study participant will continue with ABA intervention throughout the entire study.

Enrollment

Week 1-

***Daily Living Skills*:** Each participant will be given the Vineland Adaptive Behavior Scale (VABS-III). It assesses personal and social functioning for those up to 90 years of age, administered to a parent or caregiver using a semi-structured interview format. **The Medical History and Medication History will be obtained.**

Week2- 4

***Cognitive Profile*:** Results of cognitive testing (in IEP or psychological report provided by parent). A Leiter 3 cognitive assessment will be administered to study participant if the participant does not have a recent cognitive assessment (within past 3 years). ..

Desensitization: Participants will be introduced to the tDCS equipment. Most participants may require desensitization to the tDCS equipment (see Potential Problem section) to the tDCS. Desensitization to the tDCS equipment will be provided by Dr. Yoo.

Baseline Assessment 1

1. Resting EEG
2. Parent completed questionnaires
   a. Behavior Rating Inventory of Executive Function (BRIEF)

b. The Pervasive Developmental Disorder Behavior Inventory (PDDBI)
3. ABA data for skills acquisition and target behavior for weeks 1-4
4. Randomizations to sham or tDCS

****

Phase A or B- Weeks 5-8

Weeks 5-8

- 20 sessions of active or sham tDCS stimulation (depending on order assignment) – five sessions per week
  - EEG – resting EEG after tDCS #20
  - BRIEF, PDDBI,
  - ABA data for skills acquisition and target behavior for weeks 5-8

****

Baseline 2: Washout and Crossover – Weeks 9- 12(subject continues ABA therapy)

Weeks 9-12

- EEG before tDCS session end of week 12
- BRIEF, PDDBI end of week 12
- ABA data for skills acquisition and target behavior for weeks 9-12

****

Phase B or A – Weeks 13-16

Weeks 13-16

- 20 sessions of active or sham tDCS stimulation (depending on order assignment)
  - Resting EEG after session #40 tDCS or sham
  - BRIEF, PDDBI end of week 16
  - ABA data for skills acquisition and target behavior for weeks 13-16

Washout- Weeks 17-20 (subject continues ABA therapy)

Weeks 17-20

- Resting EEG after week 20
- BRIEF, PDDBI week 20
- ABA data for skills acquisition and target behavior for weeks 17-20

****

Schedule of Measurements per Study Phase TABLE 2

PHASE		Enrollment	Baseline 1`	**Phase A (active or sham)**	Crossover/ Baseline 2	Phase B (active or sham)	Baseline 3
Time		Week 1-3	Week 4	Week 8	Week12	Week 16	Week 20
Consent		X					
Medical History		X					
Leiter-3*		X					
Vineland-III		X					
Caregiver tDCS training		X					
Desensitization		X					
Randomization		X					
BRIEF			X	X	X	X	X
PDDBI			X	X	X	X	X
ABA program DTT data			X	X	X	X	X
EEG 2-5 min of continuous recording during rest.			X	X	X	X	X

**Completed for subjects that do not have a cognitive assessment within the past 3 years*

B. Study Duration

Subjects will participate in the study for 20 weeks.

C. Endpoints:

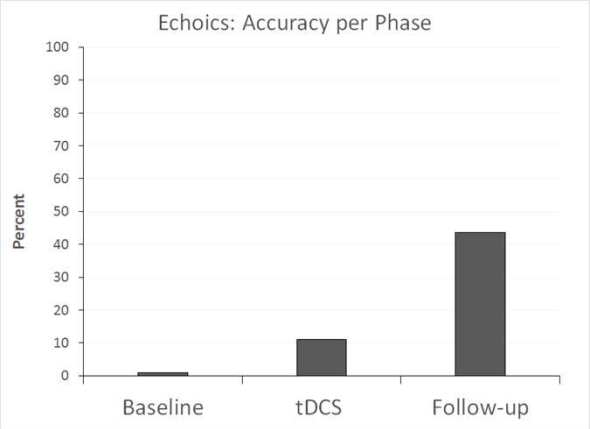
20 sessions of active and sham tDCS stimulation

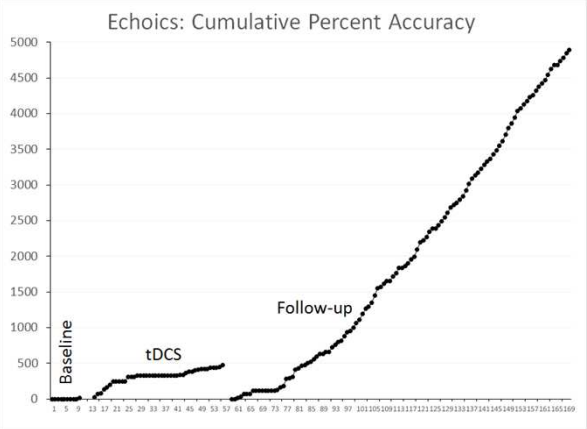
1.4 Preliminary Data

Research team: Case Reports

Case A is an 11-year-old nonverbal boy with ASD. He attends an after-school ABA program. He was referred by his mother for the absence of speech as well as difficulty with attention. Based on the referral concerns, we targeted cathode at F4 and anode at F3 for 20-mins at an intensity of 1mA for 20 minutes for 9 sessions, followed by 5 additional sessions at 1.5mA during his ABA program. No side effect was observed.

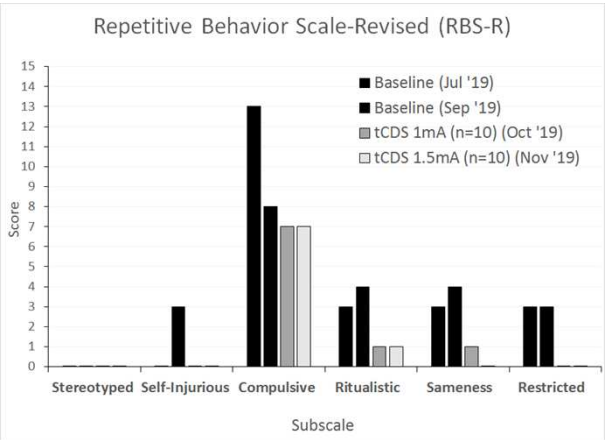
Our direct observations and parental and staff report indicate an increase in the accuracy of discrete trial performance in the areas of vocal imitation (echoics), oral-motor imitation, as well as an increase in spontaneous manding. Below are the data from his echoics program. This program was discontinued in 2016 because of lack of progress despite several years of ABA therapy. The ABA provider re-introduced the echoics program and collected baseline data prior to tDCS. These data were shared at the end of the follow-up period (last data point) and analyzed post-hoc. Results show that on average, the accuracy was 1% during baseline, 11% during tDCS stimulation, and 44% during follow-up trials. The cumulative percent accuracy shows the slope of each phase. Compared to the flatness of the baseline phase, tDCS phase shows relative increase accuracy, while during the follow-up, the slope of the cumulative is noticeably steeper, suggesting that tDCS may facilitate speech acquisition.

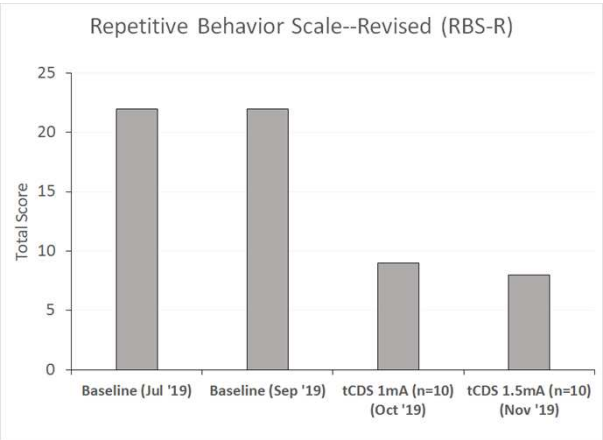




Case B is a 54-year-old woman with intellectual disability and obsessive-compulsive disorder (OCD) that began in her late teens. These behaviors included: emptying and restocking the refrigerator, emptying cans, jars, and containers, and sorting through trash. If denied access to the items, she made verbal threats and became aggressive. Because B's mother was in search of a behavior therapist to treat her OCD and we wanted to wait until a therapist was identified in order to combine behavior therapy with tDCS, we used this waiting period to collect baseline RBS-R. When her mother was unable to identify a behavior therapist after two months, we agreed to move forward with tDCS alone. We administered the second RBS-R, which served as the second Baseline. We then trained her mother to apply tDCS at home, which took less than 15 mins in our office. We then collected RBS-S after 10 tDCS sessions at 1.0mA. Because of lack of change in compulsive behaviors, we increased the intensity to 1.5mA for additional 10 tDCS sessions.

We placed the cathode on the left supraorbital (FP1) and the anode at the center occipital (OZ). The results show that there was a decrease in compulsive behaviors between the first and second baseline. tDCS did not further reduce the compulsive behaviors. However, Ritualistic, Sameness, and Restricted subscales all showed a decrease following the tDCS sessions. The total RBS-R scores also show a difference between the two baseline and the post-tDCS phases, indicating that there was a reduction in repetitive behaviors. No side effect was reported.





1.5 Sample Size Justification

This is a pilot study. Long-term objective for this proposal will be to accumulate treatment outcome data, EEG biomarker data and safety evidence, to warrant an adequately powered clinical trial

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Subjects will continue to receive their ABA therapy provided by their regular therapist as standard of care. Subjects will be randomized to begin with either sham or tDCS treatment and then cross over to the other treatment arm. Each subject with receive tDCS or sham however the order will be different in the two groups. The active tDCS and sham are procedurally identical.

B. Dependent Variables or Outcome Measures:

AIM 1: The following data will be used as outcome measures at the end of each phase of the study.

Primary The use of rating scales, completed by parents and teachers, measuring overt behavior is an often used and well-established method for assessing various domains of social, emotional, and behavioral functioning and treatment outcomes. As we are targeting the prefrontal areas, the primary outcome measure will be the **Behavior Rating Inventory of Executive Function (BRIEF),** a test that has normative data for children aged 2 to 90 years. It has parent versions containing 63 (preschool age) 86 (school age) items, taking approximately 10 to 15 minutes to complete. Each item score is converted within each scale for computation of T scores. The BRIEF contains eight subdomains of executive function: 1) Inhibit, 2) Shift, and 3) Emotional Control subdomains together result in an additional composite Behavioral Regulation Index (BRI). The subdomains 4) Initiate, 5) Working Memory, 6) Plan/Organize, 7) Organization of Materials, and 8) Monitor provide a composite Metacognition Index. The BRI and MI are also combined to obtain an overall Global Executive Composite (GEC).

- **Secondary**

  Our secondary outcome measure will be the **Pervasive Developmental Disorder Behavior Inventory (PDDBI)** and the Discrete Trial Training (DTT) data from the participant's ABA programs.

  The **Pervasive Developmental Disorder Behavior Inventory (PDDBI)** is an informant-based assessment that was standardized on a large, well-diagnosed sample of children with ASD, ages 1.5 to 12.5 years. The PDDBI assesses the effectiveness of treatments in terms of Response to Interventions (RTI). It is also used to differentiate ASD from other conditions. Both teacher and parent rating forms are available consisting of 86 items, taking about 30 minutes to complete. The PDDBI measures both adaptive and maladaptive behaviors related to ASD. It consists of the following Approach/Withdrawal Problems: 1) Sensory/Perceptual Approach, 2) Ritualisms/Resistance to Change, 3) Social Pragmatic Problems, 4) Semantic Pragmatic Problems, 5) Arousal Regulation Problems, 6) Specific Fears, 7) Aggressiveness. Under Receptive/Expressive Social Communication Abilities, there are 1) Social Approach Behaviors, 2) Expressive Language, and 3) Learning, Memory, and Receptive Language.

  Discrete trial training (DTT) is an evidence-based instructional method used to teach skills in a planned, controlled, and systematic manner (Smith, 2001). DTT is a widely used method within ABA, especially when teaching a behavior in small, teachable steps. DTT data will be collected from the participant's ABA programs for the 5-month duration of the study. The data collected will be delineated by the study phases (i.e., dates). Cumulative skill acquisition during each phase will then be analyzed and graphed. We expect steeper slope of the graph with better skill acquisition, while lack of skill gain will show a flat slope.

AIM 2: EEG data

EEG coherence measure is a useful indicator of cortical connectivity between functional areas in the brain. High coherence indicates a high level of synchronization between the two brain areas, whereas low coherence indicates a low level of synchronization. It has been shown that different EEG frequency bands correlate with different cognitive and emotional processes. EEG signals collected from the 19 standard 10-20 montage electrode positions will be used (Fp1, Fp2, F3, F7, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2). Continuous sample segments of 30 seconds will be selected from the processed resting state data and used to compute nonlinear digital biomarker values. Features will consist of the same NDI values and frequency bands as used in Bosl et al., (2018). All EEG data will be uploaded to Research Computing servers at Boston Children's Hospital for analysis. The long-term objective for this proposal will be to accumulate treatment outcome data, EEG biomarker data and safety evidence, to warrant an adequately powered clinical trial.

1.7 Drugs/Devices/Biologics

A. Drug/Device Accountability and Storage Methods

There are 5 tDCS headsets available for use for the study. Each subject will get a tDCS headset for use during the treatment/sham phases. The units will be cleaned with alcohol wipes in between use and stored in plastic bags in the research assistant office.

The EEG systems will be kept in the storage case in the research assistant office. Prior to use for EEG recording the headset will be cleaned with a sanitizing wipe containing alcohol. The dry sensors will be cleaned individually with alcohol wipes. Subjects using semi-dry sensors will have a new disposable sensor secured for use within one hour of recording.

1.8 Specimen Collection N/A

1.9 Data Collection

A. <u>Primary Data Collection</u>- all data will be entered into a RedCap database using the participant study ID. No personal identifiers will be entered into the RedCap database.

<u>AI: Descriptive Data</u>

- **Vineland Adaptive Behavior Scales Third edition (**https://www.pearsonassessments.com **(**Sara S. Sparrow, PhD Domenic V. Cicchetti, PhD, Celine A. Saulnier, PhD). is a well validated assessment of the child's daily living skills. Dr Yoo (study psychologist) will use video-conferencing, using Q-Global On-Screen Administration (OSA) to guide the interview and score responses.as recommended by the American Psychological Association. The VABS-III is organized around four Behavioral Domains: Communication, Daily Living Skills, Socialization, and Motor Skills. The VABS-III will take approximately 60 minutes to complete. It will be completed one time during the study in the baseline 1 phase. The results will be entered into a Redcap database using the child's personal study ID. No personal identifiers will be recorded or stored
- **Leiter 3**- (https://www.wpspublish.com) (for those subjects without cognitive assessment in the past 3 years) The Leiter 3 will be performed by the Dr Yoo. in the research rooms in the Child Health Institute. The Leiter-3 is a standardized nonverbal test of intelligence and cognitive abilities appropriate for individuals between the ages of 3-75 years. The Leiter-3 has been shown to be appropriate for individuals with autism and severe cognitive delays
-

<u>A2: Primary Outcome Date (see section 1.6B for further information on these questionnaires)</u>

- PDDBI- Ira L. Cohen, PhD, and Vicki Sudhalter, PhD (https://www.wpspublish.com) a link will be sent via email for the parent /caregiver to complete the PDDBI rating scale. The parent will complete the questionnaire 5 times during the study. It takes 15 min to complete.

- BRIEF -Gerard A. Gioia, PhD, Peter K. Isquith, PhD, Steven C. Guy, PhD, and Lauren Kenworthy, PhD- (https://www.parinc.com) a link will be sent via email for the parent /caregiver to complete the PDDBI rating scale. The parent will complete the questionnaire 5 times during the study. It takes 30 minutes to complete.

B. Secondary Data Collection

- Parents/ guardians will be asked to provide educational reports such as IEP or medical records (psychological testing) that indicates subject diagnosis of ASD as well as cognitive testing (within the last 3 years) for study participants. A Cognitive assessment such as WISC/ Stanford Binet will be reviewed at either via video conferencing during the Vineland assessment (shared screen) or during a study visit at the Children's Health Institute. Data extraction onto de-identified data sheets with only participant study I.D. will be obtained by the study psychologist (Dr. Yoo). See data sheet attachment.
- **Discrete Trial Data-** ABA providers take data during therapy sessions either electronically or via paper/pen. The study psychologist will discuss with the ABA therapist the participants current programs and select those programs that target executive functioning or attention. The ABA therapist will provide copies of the ABA data sheets for these specific therapy sessions. The ABA data sheet will have only the participants study ID and will be emailed to the research assistant for further analysis by Dr. Yoo.

1.10 Timetable/Schedule of Events

TABLE 1 see above

TABLE 2

PHASE		Enrollment	Baseline 1`	**Phase A (active or sham)**	Crossover/ Baseline 2	Phase B (active or sham)	Baseline 3
Time		Week 1-3	Week 4	Week 8	Week12	Week 16	Week 20
Consent		X					
Medical History		X					
Leiter-3*		X					
Vineland-III		X					
Caregiver tDCS training		X					
Desensitization		X					
Randomization		X					
BRIEF			X	X	X	X	X
PDDBI			X	X	X	X	X
ABA program DTT data			X	X	X	X	X
EEG 2-5 min of continuous recording during rest.			X	X	X	X	X

2.0 Project Management

2.1 Research Staff and Qualifications

Drs London, Bosl ,Yoo and Zimmerman-Bier have a complementary and integrated expertise in all aspects of this research proposal and have worked together on research studies for 10 years.

Dr. Zimmerman-Bier has extensive experience as PI on Clinical Research Projects. Dr. Zimmerman-Bier will provide the PI leadership for this study including IRB submission, staff hiring and training, and all aspects of project management. Dr Zimmerman-Bier will oversee the Research Coordinator to ensure regularly scheduled team meetings and research updates to the clinical team.

Dr. London (Co-Investigator) is a child psychiatrist specializing in ASD and the head of the Autism Treatment Laboratory at the Institute for Basic Research. He has extensive clinical experience in the treatment of people with ASD. He is experienced in tDCS dosage, montage design, safety considerations, participant screening, and trial reproducibility. He has been using tDCS in clinical settings, from which the preliminary data were collected. He will provide technical assistance with IRB submission, hiring and training of staff, safety monitoring and data analysis and submission of publications. He will work with the team on future studies

Dr. Yoo is a licensed psychologist and the head of the Applied Behavior Analysis (ABA) Laboratory at the Institute for Basic Research. She is experienced in tDCS dosage, montage design, safety considerations, participant screening, and trial reproducibility. She is also experienced in behavioral treatments of individuals with ASD. She will provide technical assistance with IRB submission, hiring and training of staff, desensitizing subjects to tDCS equipment, safety monitoring, data analysis and submission of publications. She will work with the team on future studies She has collaborated with Dr. London on earlier tDCS cases.

Dr. Bosl is leading a series of projects to discover patterns in infant EEG signals that can serve as biomarkers for ASD, epilepsy, and other neurodevelopmental pathology in collaboration with Boston Children's Hospital. He runs the laboratory for neuroinformatics at Boston Children's Hospital Computational Health Informatics Program. He was also the founding director and associate professor of Health Informatics and Data Science at the University of San Francisco. He is a current collaborator of this research group in a project that involves neurodevelopment in premature infants (Rutgers University), as well as development of a very early intervention for neural impairments associated with ASD, and development of a prototype infant EEG device for primary care use. He will oversee the data management and data analysis elements of the project.

2.2 Research Staff Training

Research Staff Training:

- In order to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions, we will hold one introductory group training overview with all staff,. Each research team member will also receive instructions from the Research Coordinator and Assistants on RedCap and data entry. Dr. Yoo will train the Research Assistants on the tDCS equipment and Dr. Zimmerman-Bier and the Research Assistants will receive extensive training on the EEG system by Zeto.
- A mock run-through of all study procedures on a a fictitious participant (e.g. study staff) through all study procedures. Any need for additional training or procedure clarification will be identified..
- At weekly team meetings the PI will review the protocol and procedures, review staff knowledge and answer questions or new concerns.
- Web based videos on the set up, cleaning, and maintenance of the tDCS and EEG devices will be on the restricted research drive.
- A detailed study procedure manual, including emergency contact information will be available on a shared research drive.

2.3 Resources Available

Robert Wood Johnson Medical School is one of the professional schools of Rutgers, The State University of New Jersey. The Child Health Institute, The Pediatric and Adult Clinical Research Centers, The Pediatric Neurology Program are all part of RWJ Medical School/Department of Pediatrics.

The Department of Pediatrics at RWJ Medical School conducts many investigator-initiated and pharmaceutical industry-sponsored Phase I-V clinical research efforts throughout the campus at UMDNJ-Robert Wood Johnson Medical School. The faculty and staff are trained and experienced in conducting clinical trials in children, adolescents and young adults. RWJ Medical School has a Clinical Research Center that is available to facilitate clinical research throughout the entire campus. The Department of Pediatrics has many ongoing investigator-initiated and pharmaceutical industry-sponsored Phase I-V clinical research. The Department of Pediatrics at RWJMS will be responsible for grant administration and reporting to the funding agency

Children's Specialized Hospital is part of the Barnabas/Rutgers Healthcare system. It is the largest provider of medical services to individuals with Autism Spectrum Disorders. Families interested in the study but not eligible for enrollment can be referred to outpatient services at the families request.

Psychological/Behavioral Consultation: At the termination of the research participation (including early withdrawal), a licensed clinical psychologist (J. Helen Yoo, co-investigator) will meet with each participant and his/her family to make appropriate behavior-analytic recommendations regarding the behavioral management of severe challenging behaviors. If necessary, referrals to behavioral providers will be made, as well as referrals for support groups.

Data Systems and Data Support Staff: The RWJ Information Systems, services provided 24-hours a day, 7-days a week, 365 days a year. The RWJ has collaborated with The Department of Pediatrics to develop a comprehensive HIPPA compliant telemedicine platform. The telemedicine platform utilizes two way videoconferencing.

2.4 Research Sites and Collaborating Instiutitions

Research Site: Rutgers/RWJMS/The Child Health Institute

The Child Health Institute provides the infrastructure for research studies with Rutgers Robert Wood Johnson Medical School's Department of Pediatrics and Pediatric Clinical Research Center, The Bristol-Myers Squibb Children's Hospital at Robert Wood Johnson University Hospital, and PSE&G Children's Specialized Hospital. The faculty and staff are experienced in conducting research studies on children, with ASD. The Rutgers/RWJ Medical School Office of Research and Sponsored Programs, Clinical Research Center and Institutional IRB can provide logistical and regulatory services needed for clinical research studies. The Children's Health Institute (through the Institute for Child Development) will provide the staff office space, computers and IT support as well as the research space for this proposal.
All research activities will take place in the subject's home or via video conferencing. However, informed consent / parent training /cognitive assessment may occur in the research offices at Children's Health Institute.

Collaborative Institutions

Boston Children's Hospital

The computational and statistical aspects of the proposed project will be based within the Boston Children's Hospital Computational Health Informatics Program. Informatics Infrastructure and Information Services Department of BCH includes state-of-the-art email, a wireless and wired network throughout all BCH facilities, and technical support for all BCH-located faculty and fellows. Clinical computer systems include computerized physician order entry and full availability of data and images on and off campus through a secure VPN network.
Information Services Department (ISD) provides the physical security, hardware recovery, contingency planning, and data recovery and backup routines for all informatics services. Research data are secured through a combination of network and application-level user authentication and authorization mechanisms, and data auditing schemes are

employed by all clinical data management systems and online workspace implementations. Database and applications servers are backed-up daily, and hardware recovery and contingency plans are administered by the ISD data center.
Research Computing (RC) is devoted to the specialized computing needs of the research community at BCH. RC offers the following services: data storage and backup; desktop support and backup services; server support and administration; purchase and maintenance of scientific analysis applications (e.g. SAS, STATA); and custom application development and developer support for research-specific functions. RC also provides services for conducting webinars across multiple sites as well as electronic transmission of large data files.
Institution for Basic Research (IBR):
Institute for Basic Research (IRB is New York State Psychiatric Institute/NYSPI) – Both Drs. London and Yoo will perform research activities for this study as part of their research responsibilities at IBR. They will perform all research activities at RWJMS or via video conferencing.

3.0 Multi-Center Research

N/A

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

1. **Method to Identify Potential Subjects:** Participants will be recruited from the local New Jersey ABA providers or healthcare providers in New Jersey. New Jersey has one of the highest rates of autism in the United States. Based on the gender distribution of ASD in the population, we expect that our group will be approximately 75% male) but will include subjects from ethnic groups representative of NJ counties. We do not anticipate challenges related to recruitment.

2. **Recruitment Details:**
   a. **Identify Potential Subjects-** We will begin with a kickoff meeting with local ABA providers to discuss the study with the PI Co-Investigators and study coordinator. The meeting will be virtual using WebEx. We will also publish an informational study flyer with general study details and contact information for the study coordinator. The flyer will be distributed to ABA providers or used to publish on RWJ research website, Autism New Jersey, Autism Speaks, ABA provider websites or on other autism websites.

      - A phone line will be set up for families or ABA providers to discuss the study as well as for participants to learn more about the study and set up a telephone screening intake if interested.
      - The Research Coordinator /Research Assistants- will complete a telephone Screening (determine eligibility by inclusion and exclusion criteria) . Eligible families considering participation can ask specific questions and discuss specific study details with the research assistant or PI. Information regarding the study will be emailed to participant families to review (consent forms).

3. **Inclusion Criteria**

1. Males and females between 5 and 12 years with autism
2. Enrolled in a New Jersey ABA-based program (school or in-home) supervised by a Board-Certified Behavior Analyst (BCBA)
3. Stable medical and behavioral treatments for at least 4 weeks prior to, and during the study

4. Able to tolerate wearing tDCS as determined during a week-long daily desensitization training.

4. Exclusion Criteria

1. Any implanted metal device (heart pacemaker, cochlear implant, surgical clips, etc.)
2. Severe neurological disorders such as TBI, brain tumor, intracranial infection
3. Seizure disorder with a seizure within the last two years
4. Skull defect
5. Peripheral blindness or deafness
6. Medication that might affect tDCS: There have been a few studies concerning the effect of various medications on tDCS. Some may block and others may enhance the effects depending on many factors. The assay used to test these medications was its effect on the motor cortex after stimulation and this may not apply to our montages, however, in order to minimize the chances of having medication affect our results, we will exclude participants taking the following medications:
   a. Na or Ca channel blockers which will include all anti-seizure medications
   b. Medications that affect the NMDA receptors including dextromethorphan, cycloserine
   c. Serotonin reuptake inhibitors
   d. Dopamine stimulating or blocking medications including pergolide, bromocriptine and all antipsychotic medications
   e. Norepinephrine stimulating or blocking agents including propranolol and the stimulants
   f. Drugs that can lower seizure threshold [imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, phencyclidine, ketamine, gamma-hydroxybutyrate (GHB), alcohol, theophylline]
   g. Barbiturates, benzodiazepines, meprobamate, chloral hydrate in the past 4 weeks
7. Acute skin disease
8. History of magnetic or electrical stimulation

4.2 Secondary Subjects N/A

4.3 Number of Subjects

A. Total Number of Subjects

- Total number of subjects screened = 30
- Total Number of Subjects eligible: 24 participants eligible and enrolled
- Required Number of Subjects to Complete Research: 20 participants to complete.
-

B. Total Number of Subjects If Multicenter Study N/A

C. Feasibility

Given the number of participants receiving home-based ABA therapy in NJ, we do not anticipate difficulty with recruitment.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  - Informed consent will take place via a secure video conferencing platform such as Web-ex or Doxy.me. The consent form will be emailed/ mailed to families to review prior to the video conference and shared on screen. For those families requesting on site consenting, we will secure a research room in the Institute for Child Development.
  - Parents/guardians will be able to sign the consent All signed copies of consent will be emailed and mailed to study participant families

  .
- **Individual Roles for Researchers Involved in Consent**

- As part of informed consent, the PI or research assistants will explain the aims, methods, reasonably anticipated benefits, and potential risks of the study, as well as any discomfort that participation in the research may entail. They will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant receives.

- The participant and his/her parent, or guardian will receive sufficient time to read the informed consent form and ask questions.

- After this explanation and before entry into the study, assent and consent will be appropriately recorded by means of the participant's assent and the signed and dated consent of the participant's parent /guardian. Digital signatures will be obtained using a secure system with an encrypted identifiable signature. The Research assistant /PI obtaining consent will also sign and date the consent. A copy of the informed consent form will be given or emailed to the participant and his/her parents or guardian.

- **Ongoing Consent**

  - The study length is 20 weeks for each participant. We will have weekly contact with families throughout the study and have an opportunity to follow up regularly with subjects regarding their experience, questions or concerns regarding participation. The PI will be contacted to follow up with participants for questions/ concerns unable to be addressed by the Research Assistants.
  - In addition, during the tDCS (4 weeks) or sham treatment (4 weeks) arms we have daily contact with participants daily and will ensure there are no changes to medications or health conditions that would prevent them from continuing in the study.

- **Consent Discussion Duration**
  - The initial informed consent meeting and discussion will take at least 45-minutes. Thereafter, the consent (i.e., continuation with study participation) and the upcoming study procedures will be discussed prior to each treatment arm.

- **Coercion or Undue Influence**
  - **There is no monetary incentive for participating in this study. During informed consent it is emphasized that** participation is entirely voluntary and they can withdraw consent/assent at any time. In addition, ABA therapists will continue to provide ABA therapy regardless of participants enrollment status.

- **Subject Understanding**
  - Minors or participants who are unable to comprehend the information provided can only be enrolled after obtaining consent of his/her parent or legally acceptable representative.

- **Waiver or Alteration of Consent Process Waiver or Alteration Details N/A**
- **Destruction of Identifiers N/A**
- **Use of Deception/Concealment N/A**

C. Documentation of Consent

- **Documenting Consent**

  - Consent for subjects will be documented with the signature/ digital signature of the consent form by the subject's parent/ guardian. Digital signatures will be obtained using a secure system with an encrypted identifiable signature. The Research assistant /PI obtaining

consent will also sign and date the consent with written or digital signature. Parent/guardians will be given copies of the signed consent or emailed /mailed a copy.

- **Waiver of Documentation of Consent (i.e., will not obtain subject's signature) N/A**

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
  - Our study involves minors between the ages of 5-12 and as such we will obtain consent from their parent or legal guardian. **This research study is minimal risk to subjects and therefore informed consent of** one parent/guardian.
- **Non-Parental Permission N/A**
- **Assent Process**

➢ Minors or participants who are unable to comprehend the information provided can only be enrolled after obtaining consent of his/her parent or guardian. For subjects capable of understanding the nature of the study (typically participants with mental age of approximately 7 years of age and older), the research assistant or PI will explain the research to the extent compatible with the child's understanding. The Research assistant or PI will request the assent (affirmative agreement) of the child. If the child indicates that he or she does not want to take part in the research study, this process stops, and the subject will not be enrolled in the study

- **Documentation of Assent**
  For those subjects able to give assent, the study will be discussed through video conferencing or on site in the Child Health Institute research room. In the signature block the subject will sign and date (written or electronically) or the RA will document if Assent of the child was obtained verbally.

- **Reaching Age of Majority During Study N/A**

B. Wards of the State N/A
Research Outside of NJ Involving Minors N/A

C. Non-English-Speaking Subjects N/A

D. Adults Unable to Consent / Decisional Impaired Adults -N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses
There will be no cost to the participant and his/her family for participating in this study. Parking costs will be reimbursed for study visits that require the participant and/or his/her legally acceptable representatives to be present at RWJMS,

B. Compensation/Incentives- N/A
C. Compensation Documentation N/A

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects-Reasonably Foreseeable Risks of Harm

.

The safety of tDCS is remarkable, compared to nearly any other biologic treatments which have been used. In a review of over 30,000 treatment episodes, there were no serious side effect noted (Bikson, Grossman et al., 2016). Safety in children has also been addressed and is comparable to adults, The most common side effect is a tingling feeling under the electrode (which is short lived) in about 10% of children. Over time children will get used to the tingling. About 5% of children report some temporary itching or reddening under the electrode (Krishnan, Santos et al., 2015). The redness should dissipate within five minutes. Parents and therapists will be instructed to look for any rashes to keep the child from touching or picking at the area.

B. Risk of Harm from an Intervention on a Subject with an Existing Condition

tDCS is a considered a safe and tolerable procedure. This research presents the prospect of direct benefit to the individual participant, and there is evidence that tDCS improves learning and improves the core symptoms of ASD as well as co-morbidities. The risk to participants is minimal compared to benefits. In addition, participants will be monitored throughout the study for tolerability, any side effects, or changes in health.

All participant families/guardians will meet with Dr Yoo regarding how to set up the tDCS system via video conferencing or at the research room in Child Health Institute. However, even with desensitization some children with ASD still experience difficulty tolerating different materials or equipment such as tDCS. For example, they may remove the headset, or may be more prone to pick at their skin. Children having difficulty tolerating the tDCS with behaviors will have a consultation with Dr. Yoo and the desensitization protocol will be reviewed. For subjects with behaviors such as crying for more than 5 min, refusal to wear the tDCS or displaying difficulty participating in ABA programs with tDCS or concerns regarding tolerability will be removed from the study. In addition, participants will be examined prior to and after each tDCS session for any skin irritation.

C. Other Foreseeable Risks of Harm

Subjects may experience mild discomfort during EEG cap placement. Subjects having difficulty tolerating the EEG device i.e. crying for more than 5 min or continued removal of the device will be able to continue with the study without the EEG. This will be recorded as a protocol deviation.

D. Observation and Sensitive Information

Sensitive information may be disclosed during study visits, ABA sessions and during video conferences. Unless the information relates to direct harm or neglect of those involved, all information will be held confidential.

E. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects N/A

F. Risks of Harm to Non-Subjects N/A

G. Assessment of Social Behavior Considerations N/A

H. Minimizing Risks of Harm

Dr Yoo (study psychologist) will ensure participants are comfortable with wearing the tDCS and that parents can set up the equipment easily. Before each session research assistants will ensure that participants health was unchanged prior to administering each tDCS session. tDCS will be held during illness or other concerns. The study personnel will observe the tDCS placement and removal for each session.

The treatment will be discontinued when the child participant is crying (more than 5 min), is pulling at the device or equipment, or asking to stop, . Parents and therapists will be instructed to monitor for redness under the electrode site and to keep the child from touching the area (i.e. cover with band aid).

I. Certificate of Confidentiality N/A

J. Provisions to Protect the Privacy Interests of Subjects

To minimize potential risks associated with privacy, each participant will be assigned and identified by a number. The key linking the participants' identifying data (e.g., name, DOB) and the participant number will be kept separately by the PI in a secure location. Data will be recorded, a manner that does not allow participants to be identified, either directly or through identifiers linked to them

K. Potential Benefits to Subjects

Potential benefit of tDCS is an improvement in executive function skills, decrease in the core symptoms of ASD, and/or greater learning acquisition during ABA therapy in study participants.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA) N/A

5.2 Family Educational Rights and Privacy Act (FERPA) N/A

- We will review educational records from the parents or legally acceptable representative, when available. We will not be requesting any records from the participant's school. These records may include individual educational plans or psychological evaluations. We will only record results of recent psychological testing in RedCap using the patient identifier. We will not copy / keep any of these records.

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

A. Special Populations

- This study includes minors with developmental disabilities, however, does not involve greater than Minimal Risk to participants. tDCS has been used in research studies with both children and adults as well as with individuals with and without cognitive disabilities. This procedure presents the prospect of direct benefit for the individual participant compared to the minimal risk which will be monitored by the research team throughout the study. For example, it has been shown that children in school or ABA programs can plateau at some point and have difficulty learning despite intensive one on one teaching using ABA. tDCS has been shown to improve learning in children with autism.
- Our team has extensive clinical experience with tDCS and has not encountered any difficulty with the tolerability of the treatment.
- Participants will be exposed to the tDCS treatment system before randomization and families will be trained on how to enable the participant to feel comfortable with the procedure. Participants can withdraw from the study at any time.
- The participants will be between the ages of 5-12 years old. For those participants with a mental age > 7, assent will be obtained for the study as well as parent consent. Participants will be explained about the research in non-scientific terms compatible with his/her understanding.

5.4 General Data Protection Regulation (GDPR) N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent) N/A

6.0 Data Management Plan

6.1 Data Analysis

Analysis of the data in this study will follow the approach described in Wellek, S., and M. Blettner (2012). The following steps are required:

1. Baseline analysis to check the assumption of negligible carryover effects. This test has to be performed like an ordinary unpaired t-test

.2. Test for differences between treatment effects. Formally, this test is carried out according to the same scheme as the pre-test. The crucial difference is that the customary formula for the unpaired t-test are now applied to the within-subject differences
3. Significance decisions: The significance of the difference between two treatments (tDCS and sham) is determined as well as the significance of carryover effects (step 1).

These steps are described in more detail below.

Baseline Analysis

For descriptive purposes, summary statistics of the demographic and outcome variables will be calculated. To ensure pre-stimulation (i.e., baseline) equivalence between participants assigned to the two treatment orders (i.e., sham-active vs. active-sham), the outcome measures obtained during the first baseline period (first baseline assessment session) between these groups will be compared using independent *t*-test comparisons. The primary dependent variable will be the BRIEF; fixed factors will be the treatment order (active-sham versus sham-active), and treatment condition (active and sham condition) and the secondary dependent variable will be the PDDBI. We note that, as described previously, the BRIEF will be used to assess executive functioning and the PDDBI is used to differentiate ASD from other conditions as well as to assesses the effectiveness of treatments in terms of Response to Interventions (RTI). The goal of this baseline assessment is to establish the equivalence of the two groups prior to intervention on the basis of the two outcome assessments.

In addition to summary statistics for the baseline assessments, nonlinear EEG features will be computed before testing for all subjects. Machine learning classifiers will be used to demonstrate that the two groups are equivalent and cannot be distinguished based on nonlinear EEG analysis (see Bosl et al., 2018).

Hypothesis Testing

As described briefly above, an unpaired t-test is applied to the within-subject differences for the outcomes of interest. We note that two summary outcome scores can be used (BRIEF and PDDBI), as well as for subscores. Because the subscores and the total scores are not independent, a Bonferroni correction is likely too strict and not warranted. Total scores and subcategory scores on each assessment will be tested for significant changes over time. The dependent or outcomes to be measured for within-subject differences within each group assignment (or treatment order: active-sham versus sham-active), treatment condition (active versus sham), and time (baseline and 4-week follow-up) will be the dependent variables. Independent variables will be group assignment, treatment condition, and time. The differences over time in either active or sham condition will be carried out using independent measures ANOVA. For all analyses, P values less than 0.05 will be considered statistically significant. Analyses were completed using standard R software.

EEG as a Biomarker for Treatment Outcome

The signal or time series from each sensor will be decomposed into multiple frequency bands using a wavelet transform (Walker, 2008). We note that the Haar wavelet transform yields a multiscale decomposition that is mathematically equivalent to the coarse-graining procedure first introduced by (Costa, Goldberger, & Peng, 2005) for multiscale entropy analysis of biological signals. The use of wavelets for multiscale signal decomposition and relationship of scale to traditional EEG frequency bands is discussed in (Bosl et al., 2018). Using the wavelet transform, each sensor signal will be decomposed into power-of-two frequency bands that are approximately equal to the commonly used definitions of delta, theta, alpha, beta, gamma, and gamma+ bands used for EEG analysis. The specific software used for the wavelet transform is publicly available, along with instructions and python code, at: https://pywavelets.readthedocs.io.

Several nonlinear values will be computed on multiple scales for every sensor, including sample entropy, Lyapunov exponents, detrended fluctuation analysis (DFA), and correlation dimension (CD). These will be computed on multiple scales using publicly available software "*Nonlinear measures for dynamical systems"* or nolds, version 0.3.2, which can be downloaded from (https://pypi.python.org/pypi/nolds).

Nonlinear values derived from Recurrence Quantitative Analysis (RQA) will be computed. RQA is an empirical approach to analyzing time series data that is in principle capable of characterizing all the essential dynamics of a complex system. It has been found to be useful for analyzing "real-world, noisy, high dimensional data" (Webber & Zbilut, 2005). Software for computing recurrence plot statistics is publicly available python package pyRQA 0.1.0 (Marwan, 2012). At least seven of the most commonly used recurrence plot values (RR, DET, LAM, L_max, L_entr, L_mean, and TT) will be computed and used in this study. These values have proven to be potential biomarkers for autism (Bosl et al., 2018) and absence epilepsy (Bosl et al., 2017) in our previous studies.

EEG analysis will first determine significant group differences between actual and sham tDCS for each of the nonlinear signal features computed. We hypothesize that significant changes will be observed in the nonlinear signal features. A Bonferroni correction will be required for the set of nonlinear measures. In addition to feature comparisons, regression models will be computed using the nonlinear EEG features as input variables and the change in assessment scores as output. Linear regression and machine learning regression models will be used.

Taken together, these analyses will provide the information necessary to determine if tDCS significantly improves the efficacy of behavioral therapy for improving cognitive function in children with ASD. In addition, the usefulness of EEG as a tool for measuring the changes in brain function due to tDCS augmented behavioral therapy will be determined.

6.2 Data Security and Quality

6.2a Training and Safeguards

All study personnel will receive training prior to start date of the study. There will be a kick-off meeting with the PI and Co PIs as well as research assistants. All study-related staff will receive data safety and confidentiality training. Research Staff will ensure the identity of the participants and data collected remains confidential. The following safeguards will be implemented to maintain human subject confidentiality:

- Each participant will be given a unique study identification number. These identifiers will be transcribed into a logbook with corresponding subject name. The logbook will be kept in a locked cabinet in the PI's office. In addition an excel spread sheet will be kept i(n the research folder of the restricted pediatric drive) with the study ID and subject name. Only the study coordinator and research assistants/PI will have access to this drive.
- Only the personal study ID will be used on data collection sheets where clinical data will be transcribed. Data collection sheets may be stored in the subject's binders until entered into RedCap and then destroyed. The subject folders only have the subject ID
- School reports such as IEP or psychological testing will be reviewed by the study psychologist and research assistants but not copied or stored in research binders. Psychological testing data will be extracted onto data sheets with the participants ID but without personal identifiers.
- Information from the data collection sheets (using only subject unique ID) will be entered into the RedCap database which will be secured with password protection. Data collection sheets may be stored in the subject's binders until entered into RedCap and then destroyed.
- Subject data will be entered into a password-protected database RedCap Database.
- Subject's parent and legal guardian will complete behavioral data (i.e., questionnaires) online through RedCap. Each participant will be emailed a link which opens to a behavioral form with subject ID and no identifiers. Once the form is completed by the family member, it is automatically uploaded to the

RedCap database. Subject parent and legal guardian will not be able to view the database or other subject files.

- Any publication will not include any identification of the study participants.
- The link between the subject unique I. D .and subject names will be destroyed after the completion of data collection and data analysis.
- The study data will be kept in a RedCap database for a minimum of 6 years after study closure or publication of the data.
- Confidential information obtained through written consent will be held exclusively by the study's investigators and will in no way influence the access to and quality of medical care provided.
- The PIs and the study staff will review all data on an ongoing basis for data completeness and accuracy. Data verification will be performed by someone other than the individual originally collecting the data.

6.2b Data Security

- Study personnel whose responsibilities require access to personal health information will keep the identity of the participants and data related to the study confidential. The data will be stored in a locked cabinet within a locked office. The information on the data collection sheet will be entered into a password-protected database RedCap Database with access limited to the study staff. The data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The REDCap application is a secure web application for building and managing online databases. REDCap can be installed for compliance with such standards as HIPAA, 21 CFR Part 11, FISMA and international standards. Access to the computerized data will be strictly limited to study investigators approved by the Institutional Review Board, except as required by law.
- For questionnaires that are collected and transmitted through the internet, the participant parent or legally acceptable representative will have the participant's assigned code, rather than name, when submitting the data. There are no foreseeable risks to participation except for the remote possibility that the responder's email or IP address would be inadvertently disclosed.

6.3 Data and Safety Monitoring
Our study meets the NIMH definition of minimal risk.

6.3aData/Safety Monitoring Plan

Our study meets the NIMH definition of minimal risk (i.e., the probability and magnitude of harm or discomfort anticipated in the research risks is no more than minimal risk (SEE ATTACHMENT LETTER). Our subjects are Autistic Children who present with unique communication and sensory challenges. Therefore, we have included the data and safety monitoring procedures to be followed by the research team. The PI will ensure surveillance protections are in place to ensure safety and to report any adverse events to the IRB promptly.

- Prior to enrollment all parents / caregivers with be trained on how to put on the tDCS device. Dr Yoo will work with families having difficulty with placement or to help desensitize subjects to the tDCS equipment. Subjects will also be introduced to the EEG system and if needed, Dr Yoo will help participants feel comfortable with the headcap.

- Each subject will have their own tDCS device to use for the duration of the trial. All tDCS sponges are disposable and the system can be easily cleaned and stored between use by the parents. The tDCS will be returned to the Research Coordinator at subjects' completion of study. The tDCS headband can be cleaned with alcohol and placed in a sealed bag that is signed by cleaner / cleaning date. Study visits will be by video conferencing when possible. Equipment will be sent

to subjects via Fed- Ex or courier. Rutgers University screening and testing procedures for prevention of CoVid19 will be followed.

- A study staff will conduct the entire tDCS procedure and train the parents until the parent is fully able to apply the headset and use the device. Typically, this parent training is completed in approximately 30-mins through a review of a written instruction and modeling from the staff. The research assistant will also review the safety precautions with the parent, including instantaneous disconnection and proper power off procedures. Based on the 30,000+ sessions reported in the literature, tDCS was deemed safe, even in young children.
- Then, the parent conducts the tDCS procedure under the supervision of the study staff (via telemedicine portal).
    - Once trained, the tDCS device will be placed on the subject by the parent. (Note that self-administration of tDCS is quite routine practice in other clinical applications of tDCS. In fact, the device we are using was developed specifically for home use.)
    - A member of the study team will observe the placement and removal of the tDCS device for each ABA session via video conferencing. The treatment will be discontinued when the child participant is crying (more than 5 min), is pulling at the device or equipment, or asking to stop, or if not participating in therapy. Information will be recorded on the treatment log.
- Parents and therapists will be instructed to monitor for redness under the electrode site and to keep the child from touching the area (i.e., cover with band aid). Any redness persisting greater than 2 hour or if there are any signs of skin abrasion/ lesion will be considered an adverse event reportable to the IRB.
- tDCS will be suspended during illness such as viral illness with fever, if there are skin irritation requiring medical treatment or if the child is being evaluated for new neurological or medical conditions i.e., seizures / diabetes.
- Subjects may become be discharged from the study if there are changes in their medical history/ /medication treatment (ex. a new medication is prescribed that makes the participant ineligible). Following this training, the parent will be able to conduct the entire tDCS procedure independently. In certain cases that require additional assistance, a study staff will be available through the telemedicine portal to assist the parent during the sessions. We do not anticipate that many parents will require more than 1-2 training sessions
-

6.3bData/Safety Monitoring Board Details N/A

6.4 Reporting Results

A. Individual Subjects' Results N/A

B. Aggregate Results

Findings from the study such as abstracts or papers/presentations can be shared with all participants who express an interest in receiving a summary.

C. Professional Reporting

Preliminary research analysis and project related progress will be shared with the New Jersey Governor's Council for Medical Research and Treatment of Autism in quarterly and annual reports and research meetings. We will disseminate our research findings at professional meetings and publications in discipline-related journals.

D. Clinical Trials Registration, Results Reporting and Consent Posting

The study will be registered at www.clinicaltrials.gov.

6.5 Secondary Use of the Data N/A

7.0 Research Repositories – Specimens and/or Data N/A

8.0 Approvals/Authorizations

Letters of Cooperation with Institute for Basic Research as well as Boston Children's Hospital.

.

9.0 Bibliography

Akil, H., S. Brenner, E. Kandel, K.S. et al. (2010). The future of psychiatric research: Genomes and neural circuits. Science 327 (5973): 1580–1581.

Amatachaya, A., N. Auvichayapat, N. Patjanasoontorn, C. et al. (2014). Effect of anodal transcranial direct current stimulation on autism: a randomized double-blind crossover trial. Behavioural Neurology.

Bikson, M., P. Grossman, C. Thomas, A. et al. (2016). Safety of transcranial direct current stimulation: evidence based update 2016." Brain stimulation 9(5): 641-661.

Bosl, W., A. Tierney, H. Tager-Flusberg & C. Nelson (2011). EEG complexity as a biomarker for autism spectrum disorder risk. BMC Med 9: 18.

Bosl, W. J., Tager-Flusberg, H., & Nelson, C. A. (2018). EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach. Scientific Reports, 8(1). https://doi.org/10.1038/s41598-018-24318-x

Bruce, E. N., Bruce, M. C., & Vennelaganti, S. (2009). Sample entropy tracks changes in electroencephalogram power spectrum with sleep state and aging. J Clin Neurophysiol, 26(4), 257–266. https://doi.org/10.1097/WNP.0b013e3181b2f1e3

Brunoni A. R., Amadera J., Berbel B. et al. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Neuropsychopharmacology, 14, 1133–1145. 10.1017/S1461145710001690

Casanova, M. F., Hensley, M. K., Sokhadze, E. M. et al. (2014). Effects of weekly low-frequency rTMS on autonomic measures in children with autism spectrum disorder. Front Hum Neurosci. 8:851.

Cole, E., Enticott, P.G., Oberman, L. M. et al. (2019). The Potential of Repetitive Transcranial Magnetic Stimulation for Autism Spectrum Disorder: A Consensus StatementBiological Psychiatry, 85(4), e21 - e22

Corbett, B. A., Constantine, L. J., Hendren, R. et al. (2009). Examining executive functioning in children with autism spectrum disorder, attention deficit hyperactivity disorder and typical development. Psychiatry Res, 166(2-3):210-22. doi: 10.1016/j.psychres.2008.02.005.

Costa, M., Goldberger, A. L., & Peng, C. K. (2005). Multiscale entropy analysis of biological signals. Phys Rev E Stat Nonlin Soft Matter Phys, 71(2 Pt 1), 21906.

Costanzo, F., Menghini, D., Casula, L. et al. (2015). Transcranial direct current stimulation treatment in an adolescent with autism and drug-resistant catatonia. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 8(6): 1233-1235.

Donaldson, P. H., M. Kirkovski, N. J. Rinehart & P. G. Enticott (2018). Autism-relevant traits interact with temporoparietal junction stimulation effects on social cognition: a high-definition transcranial direct current stimulation and electroencephalography study. European Journal of Neuroscience 47(6): 669-681.

Eaves, L. C. & H. H. Ho (2008). Young adult outcome of autism spectrum disorders. Journal of autism and developmental disorders 38(4): 739-747.

English, MCW, Kitching, ES, Maybery MT, & Visser TAW. (2018). Modulating attentional biases of adults with autistic traits using transcranial direct current stimulation: A pilot study. Autism Res. 11(2), 385-390. doi: 10.1002/aur.1895. Epub 2017 Nov 20.

Ewen, J. B., Sweeney, J. A., & Potter, W. Z. (2019). Conceptual, Regulatory and Strategic Imperatives in the Early Days of EEG-Based Biomarker Validation for Neurodevelopmental Disabilities. Front. Integr. Neurosci. doi:10.3389/fnint.2019.00045

Fein, D., M. Barton, I. M. Eigsti, E. et al. (2013). Optimal outcome in individuals with a history of autism. J Child Psychol Psychiatry 54(2): 195-205.

Fonteneau, C., M. Mondino, M. Arns, C. et al. (2019). Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials. Brain stimulation 12(3): 668-673.

Fregni, F., M. Nitsche, C. Loo, A. et al. (2015). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. Clinical research and regulatory affairs 32(1): 22-35.

Fridman, I., Cordeiro, M., Rais-Bahrami, K. et al. (2016). Evaluation of Dry Sensors for Neonatal EEG Recordings. Journal of Clinical Neurophysiology. https://doi.org/10.1097/WNP.0000000000000237

Geschwind, D. H., & Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. Current Opinion in Neurobiology. https://doi.org/10.1016/j.conb.2007.01.009

Geurts, H. M., Verté, S., Oosterlaan, J. et al. (2004). How specific are executive function deficits in attention deficit hyperactivity disorder and autism? Journal of Child Psychology and Psychiatry. 45, 836–1254.

Gioia, G. Isquith, P.K. Guy, S.C. & Kenworthy, L. (2000). Reviewed by Baron, I.S. Test Review: Behavior Rating Inventory of Executive Function. Child Neuropsychology. 6 (3): 235–238.

Gómez, L., B. Vidal, C. Maragoto, L. M. et al. (2017). Non-Invasive Brain Stimulation for Children with Autism Spectrum Disorders: A Short-Term Outcome Study. Behavioral Sciences 7(3): 63.

Kang, J., E. Cai, J. Han, Z. et al. (2018). Transcranial direct current stimulation (tDCS) can modulate EEG complexity of children with autism spectrum disorder. Frontiers in neuroscience 12: 201.

Kenworthy, L., Yerys, B. E., Anthony, L. G., & Wallace, G. L. (2008). Understanding executive control in autism spectrum disorders in the lab and in the real world. Neuropsychol Rev, 18(4): 320–338. doi: 10.1007/s11065-008-9077-7

Krishnan, C., Santos, L., Peterson, M. D., & Ehinger, M. (2015). Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 8(1), 76-87. doi: 10.1016/j.brs.2014.10.012.

Lai, M. C., Lombardo, M. V, Chakrabarti, B. et al. (2010). A shift to randomness of brain oscillations in people with autism. Biol Psychiatry, 68(12), 1092–1099. https://doi.org/S0006-3223(10)00708-0 [pii]10.1016/j.biopsych.2010.06.027

London, E. B. (2014). Categorical diagnosis: a fatal flaw for autism research? Trends Neurosci. 37:683–6. doi: 10.1016/j.tins.2014.10.003

London, E. B. (2018). Neuromodulation and a Reconceptualization of Autism Spectrum Disorders: Using the Locus Coeruleus Functioning as an Exemplar. Front Neurol. 19;9:1120. doi: 10.3389/fneur.2018.01120

Lovaas, I. O., & Smith, T. (1989). A comprehensive behavioral theory of autistic children: Paradigm for research and treatment, Journal of Behavior Therapy and Experimental Psychiatry, 20, 1,17-29

Marwan, N., Romano, M. C., Thiel, M., & Kurths, J. (2007). Recurrence plots for the analysis of complex systems. Physics Reports, 438, 237–329.

Marwan, N. (2012). www.recurrence-plot.tk.

Mohammad-Rezazadeh, I., Frohlich, J., Loo, S. K., & Jeste, S. S. (2016). Brain connectivity in autism spectrum disorder. Current Opinion in Neurology. https://doi.org/10.1097/WCO.0000000000000301

Monaia, H., & Hirasea, H. (2016). Astrocytic calcium activation in a mouse model of tDCS—Extended discussion. Neurogenesis (Austin). 2016; 3(1): e1240055. doi: 10.1080/23262133.2016.1240055

Monai, H., Ohkura, M., Tanaka, M. et al. (2016). Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun 7, 11100. doi:10.1038/ncomms11100

Nair, A., Treiber, J. M., Shukla, D. K. et al. (2013). Impaired thalamocortical connectivity in autism spectrum disorder: A study of functional and anatomical connectivity. *Brain*. https://doi.org/10.1093/brain/awt079

Nguyen, R. L., Medvedeva, Y. V., Ayyagari, T. E. et al. (2018). Intracellular calcium dysregulation in autism spectrum disorder: An analysis of converging organelle signaling pathways. Biochimica et Biophysica Acta. Molecular Cell Research, 1865, 1718-1732.

Ozonoff, S. (1995). Executive functions in autism. In: Schopler E, Mesibov G, editors. Learning and Cognition in Autism. New York: Plenum Press; 1995. pp. 199–219.

Page, S. J., Cunningham, J. A. et al. (2015). It Takes Two: Noninvasive Brain Stimulation Combined with Neurorehabilitation. Archives of Physical Medicine and Rehabilitation, 96(4), S89 - S93

Palm, U., E. Reisinger, D. Keeser, M.-F. et al. (2013). Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. Brain stimulation 6(4): 690-695.

Palm, U., F. M. Segmiller, A. N. Epple, F. J. et al. (2016). Transcranial direct current stimulation in children and adolescents: a comprehensive review. Journal of neural transmission 123(10): 1219-1234.

Paulus, W. (2011) Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods, Neuropsychological Rehabilitation, 21:5, 602-617, DOI: 10.1080/09602011.2011.557292

Pennington, B.F., & Ozonoff, S. (1996). Executive Functions and Developmental Psychopathology. Journal of Child Psychology and Psychiatry. 37(1),1469-7610.

Price, A. R., McAdams, H., Grossman, M., & Hamilton, R. (2015). A meta-analysis of transcranial direct current stimulation studies examining the reliability of effects on language measures. Brain stimulation, 8(6): 1093-1100.

Russell, J. (1997). Autism as an Executive Disorder. Oxford: Oxford University Press. How executive disorders can bring about an inadequate theory of mind pp. 256–304.

Sathappan, A. V., B. M. Luber & S. H. Lisanby. (2019). The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. Progress in Neuro-Psychopharmacology and Biological Psychiatry 89: 347-360.

Schmunk, G., Boubion, B., Smith, I. et al. (2015). Shared functional defect in IP3R-mediated calcium signaling in diverse monogenic autism syndromes. Transl Psychiatry 5, e643. doi:10.1038/tp.2015.123

Schmunk, G., Nguyen, R.L., Ferguson, D. L. et al. (2017). High-throughput screen detects calcium signaling dysfunction in typical sporadic autism spectrum disorder. Sci Rep. 7:40740. doi:10.1038/srep40740

Sokhadze, E. M., Lamina, E. V., Casanova, E. L. et al. (2018). Exploratory Study of rTMS Neuromodulation Effects on Electrocortical Functional Measures of Performance in an Oddball Test and Behavioral Symptoms in Autism. Front Syst Neurosci. 12:20. doi:10.3389/fnsys.2018.00020

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: Lessons from studies of the frontal lobes. Annual Review of Psychology 53: 401–433.

Takahashi, T., Cho, R. Y., Mizuno, T. et al. (2010). Antipsychotics reverse abnormal EEG complexity in drug-naive schizophrenia: a multiscale entropy analysis. Neuroimage, 51(1), 173–182. https://doi.org/S1053-8119(10)00157-6 [pii]10.1016/j.neuroimage.2010.02.009

Torske, T., Nærland, T., Øie, M. G. et al. (2018). Metacognitive aspects of executive function are highly associated with social functioning on parent-rated measures in children with autism spectrum disorder. Frontiers in Behavioral Neuroscience, 11, Article.

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron, 52(1), 155–168.

Van Steenburgh, J. J., Varvaris, M., Schretlen, D. J. et al. (2017). Balanced bifrontal transcranial direct current stimulation enhances working memory in adults with high-functioning autism: a sham-controlled crossover study. Molecular autism 8(1): 40.

Walker, J. S. (2008). A primer on wavelets and their scientific applications (2nd ed.). Boca Raton: Chapman & Hall/CRC.

Waterhouse, L., London E., & Gillberg, C. (2016). ASD Validity. Review Journal of Autism and Developmental Disorders 3(4): 302-329.

Webber, C. L., & Zbilut, J. P. (2005). Recurrence quantitative analysis of nonlinear dynamical systems. In M. A. Riley & G. Van Orden (Eds.), Tutorials in contemporary nonlinear methods for the behavioral sciences. National Science Foundation. Retrieved from http://www.nsf.gov/sbe/bcs/pac/nmbs/nmbs.jsp

Weeden, M., Ehrhardt, K., Poling, A. (2010). Psychotropic drug treatments for people with autism and other developmental disorders: a primer for practicing behavior analysts. Behav Anal Pract. 3(1):4–12. doi:10.1007/BF03391753

Wellek, S., & Blettner, M. (2012). On the Proper Use of the Crossover Design in Clinical Trials. Deutsches Aerzteblatt Online. https://doi.org/10.3238/arztebl.2012.0276

Welsh, M. C., & Pennington, B. F. (1988). Assessing frontal lobe functioning in children: Views from developmental psychology. Developmental Neuropsychology, 4:3, 199-230, DOI: 10.1080/87565648809540405

Wilson, J. E., Quinn, D. K. Wilson, J. K. et al. (2018). Transcranial Direct Current Stimulation to the Right Temporoparietal Junction for Social Functioning in Autism Spectrum Disorder: A Case Report. The journal of ECT 34(1): e10.

Yoo, J. H., Williams, D. C., Napolitano, D. A. et al. (2003). Rate-decreasing effects of the atypical neuroleptic risperidone attenuated by conditions of reinforcement in a woman with mental retardation. J Appl Behav Anal. 36(2):245–248. doi:10.1901/jaba.2003.36-245

Zarcone, J. R., Lindauer, S. E., Morse, P. S., et al. (2004). Effects of Risperidone on Destructive Behavior of Persons with Developmental Disabilities: III. Functional Analysis. American Journal on Mental Retardation 2004 109:4, 310-321