Christiana Care Hospital
Neurology Department

Study Protocol

Enhancement of Behavioral and Cognitive Outcomes in Autism Spectrum Disorder Via Neurostimulation

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AIMS:

Aim 1: To determine the effects of High frequency (HF) repetitive Transcranial Magnetic Stimulation (rTMS) of the inferior parietal lobule (IPL) on social/behavior deficits in children and young adults with ASD.

Aim 2: To assess the differential effects of HF rTMS of the left versus right IPL on linguistic and visual coding abilities in ASD.

Aim 3: To evaluate the effects of right/left HF rTMS stimulation of IPL on executive functioning in ASD.

BACKGROUND:

ASD encompasses a wide range of impairments in the reciprocal social and communicative skills as well as presence of restrictive and/or repetitive patterns of behaviors. The environmental, genetic, and biological etiologies for ASD are yet to be fully defined. ASD is heterogeneous in nature and thus far, numerous genetic factors have been identified in the affected children, including single gene mutations, chromosomal abnormalities, and sub-microscopic deletions or duplications, altogether accounting for approximately 10% of cases. Some authors have predicted between 350 to 400 ASD susceptibility genes. Copy number variations are also found to play an important role in developing the ASD phenotype. Abnormalities in genes involved in epigenetic regulation, including mRNA translation, have been reported in ASD. Far less progress has been made in ascertaining the contribution of environmental factors in ASD.

There is a growing body of evidence supporting the utility of rTMS in a variety of neuro-psychiatric conditions in adults and children (1, 2). Although these disorders encompass a diverse list, regardless of the underlying etiologies, the neurophysiological alteration manifests itself through under or over activation of the cerebral cortex. rTMS is a noninvasive method which induces a magnetic field in the targeted area of the cerebral cortex and hence, alters the excitability of the neurons. While low-frequency magnetic stimulation (<1 Hz) is known to suppress the cortical activity, high-frequency stimulation (5-20 Hz) enhances the cortical activity (3). Depending on the type and nature of the underlying disorder, high or low frequency stimulation may be applied to mitigate the abnormal cortical activity and therefore modulate the cortical excitability. The safety of rTMS has been the subject of a review article by Krishnan et al, who have cited 35 manuscripts pertaining to the use of rTMS in various neuro-psychiatric conditions (4).

Use of rTMS in ASD has been the subject of several extensive reviews (5, 6, 7). Aside from a few exceptions, these studies were open label and included a small number of subjects. In the majority of the studies, the rTMS parameters were quite conservative, delivering between50-200 pulses per session and yielding mixed results in behavioral rating scales or neuropsychological measures. In most cases, the bilateral dorsolateral prefrontal cortex was targeted. Low-frequency stimulation in this area has correlated with improvement in repetitive behavior. High-frequency rTMS stimulation on the premotor cortex has resulted in an improvement in motor coordination in ASD. High-frequency rTMS to the bilateral medial prefrontal cortex in adults with ASD yielded improvement in social relatedness.

The mirror neurons, concentrated in the inferior frontal and parietal lobes in humans, play a substantial role in imitating activities (8). This function is quintessential in acquiring language, nonverbal communication, empathy, social behavior and reciprocal interactions (9, 10, 11). The above attributes constitute the core deficits in children with ASD (12, 13). rTMS stimulation of the mirror neurons has not been attempted in the past.

Language, the most treasured attribute of humans, is often impaired in ASD. Stimulation of left frontal lobe has been known to improve verbal fluency in children with ASD (14). While formulating language is modulated by the left posterior frontal lobe, deciphering language is localized to the left anterior temporal lobe. As such, the mirror neurons and language centers grossly colocalize in the same regions on the left hemispheres.

Moreover, these children experience issues with attention, self-regulation, and impulse control (ADHD), all attributable to abnormalities in frontal lobe connections. Stimulation of the frontal lobe has been reported to improve attention in individuals with ADHD. There are but 2 published studies on the application of rTMS in ADHD. High-frequency stimulation of the right dorsolateral prefrontal cortex resulted in an improvement in attention (1, 2).

While in right-handed individuals the left hemisphere is solely responsible for language function, in left-handed people, bilateral representation of language function is not uncommon. Right hemispheric language dominance is extremely rare. As such, for all practical purposes, the left hemisphere is considered the dominant hemisphere for language. On the other hand, the right hemisphere modulates visual and spatial processing and reasoning.

METHODS:

This is a prospective, double blind study to examine the impact of rTMS on social behavior and cognitive outcome measures in children and young adults with ASD.

The patients followed in our neurology clinic who meet the DSM-V criteria for ASD will be given the opportunity to join this study. The diagnosis of ASD will be confirmed with the Gilliam Asperger Disorder Scale (GADS) which is a standardized questionnaire and used routinely for this purpose.

Depending upon the underlying symptoms, the patient may be receiving various drugs such as stimulants or other medications for behavioral control. We will make every effort to minimize use of medications during the period of the study. If possible, the unnecessary pre-existing medications will be tapered off. Moreover, unless the child is experiencing dangerous impulsive behavior, no new medications will be introduced during the period of the study.

INCLUSION CRITERIA:

1. Fulfilling the DSM-V criteria for ASD
2. Diagnosis of ASD confirmed by GADS
3. The patient exhibiting adequate understanding and cooperation for the procedure

EXCLUSION CRITERIA:

1. Children with ASD exhibiting significant anxiety or contact avoidance, precluding them from cooperating with the procedure
2. Children with a known diagnosis of seizures

INTERVENTION:

The rTMS treatment sessions will be scheduled 2 days a week for 5 weeks. In the beginning of each session, a single pulse stimulation will be utilized to determine the motor threshold. This is accomplished by increasing the intensity of the stimulation to achieve a twitch in the thenar muscle on the right hand. Eighty percent of the motor threshold will be applied for the treatment session. Each treatment session will consist of 10 minutes of HF rTMS delivery to the IPL, either the right or the left side, according to the paradigm detailed in the table below.

Frequency	10 Hz
Burst duration	10 seconds
Inter-burst intervals	20 seconds
Session time	10 minutes
Total stimulations per session	2000
Intensity	80% of motor threshold

The rTMS paradigm

rTMS TARGETING OF THE IPL:

For targeting the IPL, we are planning to use the standard 10/20 electrode placement system used for EEG recording. The IPL localizes to the Brodmann areas 7 and 40 and the P3/4 electrodes (15). A recent publication by Huang at al used sophisticated analysis of functional MRI and resting state functional connectivity in ASD and proposed multiple potential targets for neurostimulation including DLPFC, angular

gyrus and inferior frontal gyrus. Angular gyrus falls under Brodmann 40 and P3/4 EEG electric placement and overlaps with our proposed targeting of the IPL (16).

TREATMENT GROUPS AND THE EXPERIMENTAL DESIGN:

The patients will be randomized at the time of recruitment to either receiving left or right IPL stimulation. A standard shamming technique will be utilized to blind the patient regarding the treatment targeting (17). The neuropsychologist obtaining and interpreting the outcome measures will also be blinded. Only the clinician delivering the rTMS treatment will have a knowledge about the treatment targeting.

OUTCOME MEASURES:

A battery of neuro psychological measures will be implemented at baseline, after completion of the rTMS intervention and three months later. To assure high quality and reproducibility of the results, the testing will be completed by an experienced and board-certified neuropsychologist at Nemours A.I. DuPont Hospital for Children. Also, to make certain of the validity and authenticity of the results, the psychologist will remain blinded regarding the hemispheric targeting of rTMS. The battery of tests will consist of the following elements:

NIHTB-CB – The NIH Toolbox of Neurological and Behavioral Functioning- Cognitive Battery was constructed to embody cognitive tasks that are influential in everyday functioning (18). The NIHTB-CB has been standardized for use with children and adults ages 3-85 years of age. Recent studies have demonstrated the NIHTB-CB as a reliable and valid assessment for both adult and pediatric individuals and consist of brief tasks which are administration via IPad Two of the tasks from the NIHTB-CB, Flanker and DCCS will be utilized to assess Executive Function (EF) as described below (19, 20).

Flanker: The Flanker Inhibitory Control and Attention is a test to measure the inhibitory and attentional facets of Executive Functioning. Administration of the Flanker task is approximately 4 -5 minutes and involves a central target (arrow or fish) flanked by two additional arrows on either side. The aim is to indicate the direction of the middle stimulus. Trials include either flankers facing the same direction (congruent) or distractor flankers that face the opposite direction from the middle stimulus (incongruent).

DCCS: The Dimensional Change Card Sort is a task designed to assess cognitive flexibility. The individuals are shown an on-target image and instructed to select one of two images matching the target based on the category of shape or color. Participants matched images by each dimension independently for 10 trials (5 trials shape matching and 5 color matching) followed by set of 30 "switch" trials. Raw scores are converted to normative standard scores (mean=100, SD=15) with higher scores indicating better performance.

SRS-2: The Social Responsiveness Scale – Second Edition (SRS-2) is a 65-item, parent/caregiver-rated scale assessing social interaction and communication deficits (21). Different versions of the scale are used based on patient's age and will be administered to parents. The total scale, which is the sum of responses (rated 1 to 4), is reported here. Raw scores range from 65 to 260 and are converted to t-scores (mean of 50 and standard deviation of 10). As such, higher scores suggest worse symptoms.

RRBs: Repetitive Behavior Scale-Revised is a parent rating scale that measures restricted repetitive behaviors (22). This scale consists of 43 items that correspond to six RRB subscales: stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted. Subscale scores are calculated by summing ratings (0=behavior does not occur to 3=behavior is a severe problem) of all correspondent items, representing the severity of each type of RRB. An overall RRB score is calculated by summing the subscale scores.

D-KEFS Verbal Fluency: The Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency task is composed of three subtests 2 of which will be implemented to quantify verbal fluency: Letter Fluency, Category Fluency, and Category-Switching Fluency (23). These subsets assess speed of generating words beginning with specified letters (Letter Fluency) or words from different categories (Category Fluency).

The final subtest evaluates cognitive set-shifting (an executive function) and verbal fluency. This test has alternate forms and is normed on individuals 8 years old through adulthood. Higher scores indicate more fluent word production.

WRAML-3: Design Learning subtest from Wide Range Assessment of Memory and Learning-Third Edition is a paper-and-pencil test with six subtests assessing immediate memory recall for participants aged 5-89 years (24). For this study, the Design Learning subtest will be used to assess immediate visual memory. In this task, the participant is shown a single card across four trials. The card has 18 different geometric shapes distributed across four quadrants. It is exposed for 10 seconds and then removed; after a 10 second delay the participant is asked to recall and draw the shapes in the correct locations. This procedure is repeated three times for a total of four trials.

NUMBER OF SUBJECTS:

This is a small pilot study which will include 20-30 subjects with ASD.

DURATION OF THE STUDY:

We aim to recruit the subjects over a 2-year period. Each subject will receive the rTMS treatments 2 days a week for a period of 5 weeks and will be followed for three months after the intervention.

GENDER OF SUBJECTS:

There will be no gender preference when enrolling for this study.

AGE OF SUBJECTS:

We aim to recruit children and young adults with ASD. The subjects will be children 8 years or older and young adults up to 25 years old.

RACE & ETHNIC ORIGIN:

There will be no restrictions in enrollment based upon race or ethnic origin.

DATA ANALYSIS:

The numerical values generated by the above semi-quantitative measures (SRS, RRBs, NIHTB, DKEFS, WRAML-3) before and after treatment and after 3-moth follow up will be entered into an excel database and used for statistical analysis. For establishing statistical significance between the mean values before and after treatment, student t-test and confidence intervals will be used.

RISKS:

rTMS is a noninvasive method and not associated with any risks.

ADVERSE EVENTS:

The adverse effects of rTMS are mild and benign and consistent of transient headaches or scalp discomfort. Occurrence of seizures is quite rare; Krishnan et al. reported a total of 2 cases of seizures in 332 subjects participating in 35 trials of rTMS between 2004 and 2014. Both patients did have clear risk factors for seizures. These seizures occurred with the high-frequency stimulation of 15-20 Hz and short inter burst intervals which will be avoided in our protocol. Our study protocol will exclude all patients with history of epilepsy. Medications which may lower the seizure threshold will be avoided altogether if possible.

SEIZURE PROTOCOL:

If the patient should experience a seizure during the treatment, the following protocol will be followed

1. Universal seizure precautions and safety

2. Monitoring the vital signs

3. Calling the code and transferring the patient to the emergency room. If the seizure lasts for less than a minute, no specific treatments or interventions are necessary. However, the patient will be withdrawn from the study protocol. If the seizures are prolonged, in the emergency room, further decisions will be made regarding performing an EEG or other necessary treatments.

POTENTIAL BENEFITS TO THE SUBJECT AND SOCIETY:

Currently, there are no treatment options to mitigate The cognitive function and in particular, social cognition in patients with ASD. Based on the current research, the patients may directly benefit from the effects of rTMS on cortical modulation. If this study yields beneficial results, we will proceed with another NIH grant to fund this study on a larger scale.

METHOD OF SUBJECT IDENTIFICATION AND RECRUITMENT:

Patients who are referred to our clinic for evaluation of their developmental disabilities and confirmed to have ASD will be approached to participate in the study.

PROCESS OF CONSENT:

The informed consent will be obtained by the PI or the Co-PI's. The study setup, purpose, risks and benefits will be discussed at length with the patients/family. They will be given the opportunity to weigh their decision prior to giving/refusing consent. If consent is declined, no further effort will be made in persuading them otherwise.

Determination of Mental Competence for Consenting:

Subjects' mental competence for consenting will be determined based on the developmental milestones, in particular language development and intelligence as determined by the neurological evaluation as well as the neuropsychological assessment. The patients would be categorized into the following groups:
For all minors, 13 years and younger, parental consent will be obtained.
For teenagers ages 13-18 in addition to parental consent, an assent will be obtained.
For individuals between 18-25 years of age with mild, moderate or severe mental retardation as determined by the neuropsychological evaluation, parental constant will be necessary. If the degree of intellectual impairment is mild, an assent will also be obtained. For individuals older than 18 who are mentally handicapped, the parents need to present POA documentation in order to sign the consent form.

DOCUMENTATION OF CONSENT:

The consent will be documented in writing and the signed consent form will be kept in the patient's medical record along with a copy that will be placed in the secure research file accessible to study personnel only. The patient/family will receive a copy of the signed consent form.

COSTS AND PAYMENT:

The subject will not incur any additional costs other than those accrued from their standard evaluation and treatment. The patients will receive a stipend for participating in this research ($ To be determined)

DATA STORAGE AND CONFIDENTIALITY:

For the purposes of the research records, all of the subjects will be identified using a unique number. No identifiable health information will be publicly accessible, whether in written or electronic form. All of the obtained health information will go into a database that will be password protected and maintained indefinitely. Originals will be stored in a locked filing cabinet in the neurosciences office.

SUBJECT WITHDRAWAL:

The subjects may withdraw at any point from the study. This would not affect the delivery of the neurological care they need to receive.

LITERATURE REVIEW

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