Journal of Clinical Neuroscience 74 (2020) 151–154

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Enhancement of behavioral and linguistic outcome measures in autism spectrum disorder through neuro-navigated transcranial magnetic stimulation: A pilot study

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ARTICLE INFO

Article history:
Received 1 December 2019
Accepted 8 February 2020

1. Introduction

Autism spectrum disorder (ASD) encompasses a wide range of impairments in reciprocal social and communicative skills, as well as the presence of restrictive and/or repetitive patterns of behavior [1]. These lifelong impairments often introduce significant functional, financial, and health challenges [2]. While the environmental, genetic, and biological etiologies of ASD are not well understood [3], intense public and scientific interest in the disorder has bolstered a search for effective pharmacological and behavioral interventions [4], as well as the use of non-invasive brain stimulation via methods such as transcranial magnetic stimulation (TMS) [5]. This last approach has generated hope in the clinical community as a means of directly modulating cortical regions thought to underly behavioral function.

Individuals with autism often demonstrate failures of insight in social interactions, including difficulty in appropriately responding or engaging in social settings. This inability to correctly ascribe or interpret the intentions of others has been hypothesized to result from dysfunction of the mirror neuron system [6]. Mirror neurons are a set of visuomotor neurons which activate during the performance of specific action or the observation of another individual performing an action. Moreover, the mirror neuron system selectively responds based on the goal of an action (and not simple motor movement) providing a crucial link between action and intention [7]. Their ability to distinguish subtle implications of gestures has led researchers to suggest that mirror neurons play an integral role in acquiring language, nonverbal communication, empathy, social behavior and reciprocal interactions [8,9]. The presence of corresponding deficits in ASD has given rise to the "Broken mirror theory" [10] which proposes that mirror neuron dysfunction contributes to core deficits of the disorder [11–13].

While the mechanism by which mirror neurons are impaired in ASD are not yet known, the enhancement or restoration of mirror neuron function has been promoted as one means of improving social cognition [14]. Mirror neurons are principally concentrated in the inferior frontal gyrus (IFG) and the inferior parietal lobe (IPL) in humans [12]. The IPL in particular has been proposed to be responsible for the encoding of goals and integrating motor workflow with dorsal and ventral visual streams and coordinate with the IFG [15]. It is known that individuals with ASD are able to judge simple intentions [16], especially when contextual information is available [17]. Dysfunction of the IPL may explain why in the absence of functional/contextual information or in complex "chained actions", children with ASD may have greater difficulty recognizing intention and imitating actions of others [18]. While the bilateral-IPL function as important parts of the mirror neuron system, the left-IPL has been shown to play particular roles in gesture imitation [19], the ability to interpret other's reasoning [20], as well as important roles in language learning [21] and social cognition [22]. These common roles in the ability to interpret others through actions as well as speech, suggests that therapies attempting to enhance left-IPL function may help mitigate corresponding impairments observed in ASD.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation technique which allows the alteration

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https://doi.org/10.1016/j.jocn.2020.02.005
0967-5868/

of cortical excitability through repeated induction of neural activity [23]. The effects of rTMS depend on the paradigm applied; low-frequency (LF) stimulation (<1 Hz) is expected to suppress cortical activity and high-frequency (HF) stimulation (5–20 Hz) enhances cortical activity via mechanism of long term depression (LTD) and long term potentiation (LTP) respectively [24]. rTMS represents a promising tool in the field of neuro-psychiatry, already showing growing use in the clinic for the treatment of mood disorders [25]. Additionally, rTMS has been observed to be a well-tolerated approach for therapeutic neurostimulation in both adolescent and child populations [26–28]. As a technique which can directly modulate cortical activity with minimal side-effects, rTMS represents a developing adjunctive approach for treating the core symptoms of ASD [5].

Researchers investigating rTMS as a therapeutic approach in ASD have primarily adopted commonly used paradigms targeting the unilateral or bilateral dorsolateral prefrontal cortex, similar to approaches used in the treatment of depression [5,25]. While these approaches remain promising and have shown modest improvements in social relatedness or repetitive behaviors, targeting the mirror neurons may offer a better therapeutic option for improving social cognition [29]. In one study, Mehta et al. reported that the motor resonance properties of the mirror neuron system could be enhanced in healthy adults using high frequency rTMS to the left-IFG [30] and more recently, excitatory HF rTMS stimulation of the left-IPL has been reported to mitigate some language and social deficits in ASD children with severe intellectual disabilities [31]. We similarly had hypothesized that high frequency TMS applied to the left-IPL facilitates the cortical activity and consequently improves social behavior and linguistic abilities in children and young adults with ASD.

2. Methods

The participants were recruited from our neuroscience clinic to participate in this pilot study. The patients were evaluated for ASD via a standard diagnostic workup which included: a brain MRI study, the Autism Diagnostic Observation Schedule-2nd edition (ADOS-2), neuro-metabolic screening as recommended by the American Academy of Neurology as well as chromosome MicroArray. The study protocol and methods were approved by the Western IRB. Parents of the participants were consented using a form approved by the IRB and the children assented to participate in the trial. Depending upon the underlying symptoms, the patients may have been prescribed medications such as stimulants. We made every effort to minimize use of medications during the period of the study. If possible, unnecessary pre-existing medications were to be tapered off. Moreover, no new medications were introduced during the study period. Inclusion and exclusion criteria are shown in Table 1.

MRI images of each participant's brain were projected virtually using the Brainsight navigation system (Rogue Research Inc) and the location of the left-IPL was identified by an experienced neurosurgeon. These coordinates were saved and used to target the left-IPL in the future sessions. The treatment sessions were scheduled 3 days a week for 3 weeks. At the beginning of each session, the resting motor threshold of each participant was determined. TMS machine power was gradually increased until stimulation of the motor cortex was sufficient to elicit a twitch in the thenar muscle of the right hand. Selected stimulation strength was 80% of the identified resting motor threshold. During treatment, participants received high frequency stimulation to the left-IPL over a 5-minutes. Detailed rTMS paradigm information is presented in Table 2. Efficacy of rTMS was evaluated on the basis of the neuropsychological methods enumerated under outcome measure.

Table 1
Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Fulfilling DSM5 for ASD	Diagnosis of seizure/epilepsy
ASD confirmed by ADOS	Contact avoidance precluding them from cooperation
Absence of focal brain pathology amenable to surgery	Use of medications that lower seizure threshold

Table 2
TMS parameters for each treatment session.

Frequency	10 Hz
Burst duration	10 s
Inter-burst intervals	20 s
Session time	5 min
Total stimulations per session	1000
Resting motor threshold	80%

3. Outcome measures

ADOS-2 The Autism Diagnostic Observation Schedule – 2nd edition (ADOS-2) is a semi-structured, observation-based, standardized measure of ASD symptoms [32]. The ADOS is considered the "gold standard" for diagnosis of autism and ASD [33]. There are five ADOS-2 modules in which tasks are based on chronological age and/or language and verbal abilities. For this study, Modules 3 and 4, which are primarily used for verbal children, adolescents, and adults, were administered. For the ADOS-2, higher scores indicate greater dysfunction. The scores for modules 3 and 4 are 0–78 and 0–86 respectively. ADOS-2 was administered to the cohort at baseline and after completion of the TMS protocol.

SRS-2 The Social Responsiveness Scale – Second Edition (SRS-2) is a 65-item, parent/caregiver-rated scale assessing social interaction and communication deficits [34]. Different versions of the scale are used based on patient's age; for this study, the school-age version (for ages 4 to 18) was 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. The SRS-2 was administered at baseline, after completion of the TMS protocol and at 3-month follow-up.

EVT-2 The Expressive Vocabulary Test – 2nd Edition (EVT-2) measures an individual's expressive language skills [35]. In essence, participants are asked to provide the name or a synonym of a given picture. This standardized measure has two versions to limit test-retest effects and was normed on individuals ages 2.5 years through adulthood. The range of raw scores is 0 to 190, with higher scores indicating better expressive language skills. EVT-2 was administered to the cohort at baseline and after completion of the TMS protocol.

D-KEFS Verbal Fluency The Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency task is composed of three subtests: Letter Fluency, Category Fluency, and Category-Switching Fluency [36]. The first two 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 measure has alternate forms and is normed on individuals 8 years old through adulthood. Higher scores indicate more fluent word production. D-KEFS was administered to the cohort at baseline and after completion of the TMS protocol.

Table 3
Outcome measures before and after the intervention.

	Before mean	SD	After mean	SD
ADOS-2 Total	15.75	4.79	12.50	4.80
SRS-2 Total Raw	81.75	32.13	64.75	7.37
D-KEFS Letter	24.25	12.12	25.00	11.75
D-KEFS Category	23.25	9.14	29.75	3.78
D-KEFS Switching	11.75	3.30	10.75	2.50
EVT-2 Raw	116.00	24.83	118.50	21.33

4. Results

We recruited a total of 4 boys and the ages ranged from 11 to 17 years. The patients had been prescribed modest doses of stimulant medications at base line which was continued during the study. No other central acting medications were administered. Each patient was treated with 9 sessions of high frequency TMS targeting the left-IPL. The numerical values generated by the above quantitative measures (ADOS-2, SRS-2, EVT-2, DKEFS) before and after treatment were entered into an excel database and subjected to statistical analysis. The means and standard deviations for the study subjects before and after the intervention are shown in Table 3. Statistical changes in outcomes assessed using paired-sample t-tests performed using IBM SPSS 26.

The total ADOS-2 scores improved in three of the four subjects (mean = 15.75 prior to the intervention and 12.50 post-treatment). Statistical significance however, was not reached. On the measures of verbal fluency, D-KEFS Category Fluency subset showed trend-level significance in improvement (mean = 23.25 pretreatment and 29.75 post-treatment, $t = -2.16$, $p = 0.12$). Similarly, the total SRS-2 scores improved in three of four subjects shown in the Table 3. At the 3-month follow-up the mean decreased further to 63.67 and this improvement also showed trend-level significance ($t = -2.53$, $p = 0.13$) suggesting enduring effects of the TMS intervention.

5. Discussion

In this study, the ability of high frequency rTMS targeting the left-IPL was investigated as a means of improving core symptoms and language ability in ASD. Our study recruited a small cohort of 4 children with ASD, each treated with 9 sessions of rTMS with outcome measures taken prior to, following, and in one measure (SRS-2) three months after rTMS treatment. This study is the first study to investigate these effects within a mild-severity ASD population. While rTMS treatment improvements in mean behavioral scores were observed for most outcome measures used in this study, we were unable to reach statistical significance due to the small sample size. Despite this, we observed trend-level improvements in measures of verbal fluency as well as in social responsiveness at follow-up. Additionally, the SRS-2 completed by the parents demonstrated a modest improvement in social responsiveness which was sustained after 3 months of follow-up. These findings contribute additional evidence for the efficacy of rTMS as a means to enhance behavioral measures in ASD and suggest that such improvements may be beneficial even months after treatment.

The mechanisms by which rTMS may exert its therapeutic effects remain an area of significant investigation [37]. High frequency rTMS is expected to induce neuroplastic changes in cortical excitability within the region stimulated via LTP-like mechanisms [23]. However, in addition to changes in excitability, the application of high frequency rTMS may increase levels of brain-derived neurotrophic factor (BDNF) in the cortex [38]. BDNF is a growth factor which encourages the growth and survival of neurons [39] and white matter repair [40]. This BDNF production has been proposed as one mechanism of prolonged anti-depressant effects of rTMS [41]. Moreover, the effects of TMS are not limited to the region being stimulated and may propagate to other cortical areas via local and long-distance connections [42]. The left-IPL region stimulated in this study is strongly connected to other cortical regions by white matter tracts including the superior longitudinal fascicle (SLF) and the arcuate fasciculus (AF) [43]. In addition to connecting cortical regions of the mirror neuron system [44], the SLF is known to play important roles in the processing of affective faces [45] and the AF with visuospatial and language processing [46]. Targeting the left-IPL region in this manner thus offers the possibility of addressing not only dysfunction in the mirror neuron system, but also impairments in language and affective processing as well.

The results of this study support the findings recently reported in a cohort of eleven children with low-functioning autism (IQ < 70) [31]. In their work, Yang et al reported similar improvements in language and social relatedness on the Autism Treatment Evaluation Checklist (ATEC) which were observed six weeks after completing two HF rTMS courses also targeting the left-IPL. While similar in target area (left-IPL) and rTMS mode (HF: 20 Hz vs 10 Hz here), these studies differ primarily in treatment length (6 weeks vs 3 weeks here) and target population. One innovation introduced in our study was the inclusion of highly individualized rTMS therapies using MRI-based neuro-navigation to localize the left-IPL. Importantly, our protocol intentionally excluded patients with severe ASD and contact avoidance, as the patient's cooperation was necessary for the purpose of TMS localization. Issues with contact avoidance and lack of cooperation are significant impediments to studying children with ASD. For instance, Yang et al deferred measurements of motor threshold for the same reason and estimated the location of the left-IPL on the scalp. Despite these differences, the apparent response of patients in terms of language and social responsiveness suggests that further exploration of this approach is merited.

The conclusions here are accompanied by a number of important limitations, including the lack of any sham stimulation methods or control groups which may be used to account for placebo effects. Our results concur with the similar approach reported by Yang et al, but we note that the exploratory sample size used in our work restricts the statistical power to independently test hypotheses regarding the effect of the treatment. Even with these limitations in mind, this study supports the safe and practical use of rTMS within a mildly-impaired ASD population and represents the first use of neuro-navigated rTMS targeting the mirror neuron system in any ASD population. Future studies are needed to establish the efficacy of this approach in a larger subject pool, preferably employing a randomized control design.

In conclusion, rTMS is a promising intervention which may help improve behavioral and linguistic outcomes in ASD. Our results here add additional evidence that specifically targeting the mirror neurons in the left-IPL potentially improves measures of social responsiveness and language ability. To further confirm the therapeutic effects of TMS in children with ASD, additional studies with larger sample sizes are necessary. Together with research investigating the therapeutic effects of rTMS and the neurobiological underpinnings of ASD, these research directions may eventually allow highly individualized neurostimulation approaches to treatment. With convergent technological developments, the use of rTMS may be available for ASD patients for home use, similar to what is now available for self-management of migraines [47].

Acknowledgements

The authors would like to express their gratitude to John Medaglia, PhD (Department of Psychology, Drexel University) and Kam-

biz Pourrezaei, PhD (Department of Biomedical Engineering, Drexel University) for their contribution to the development of this project.

The authors greatly appreciate the technical and logistical contributions made by Noelle McClure, RN and Amy Black.

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