Original Article

Low-frequency Prefrontal Cortex Magnetic Stimulation Improves Autism Spectrum Disorder Symptoms: A Pilot Study

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Abstract

Aim: Autism spectrum disorder (ASD) is a common neurodevelopmental disorder affecting multiple levels of social and cognitive skills and causing a significant health-care burden. Currently, there is no approved treatment for ASD. **Methods:** In this study, 10 children with ASD between the ages 6 and 19 years (M = 12.3, standard deviation = 3.94) were recruited. Repetitive transcranial magnetic stimulation (rTMS) was applied and symptom severity was measured before and after treatment using the Childhood Autism Rating Scale (CARS) and Autistic Behavior Checklist (ABC). All children received sessions of low-frequency rTMS to the bilateral prefrontal cortices. **Results:** The results showed that the children improved according to both symptom ratings. Specifically, both the relating ($z = -2.02$, $P < 0.05$), body and object use ($z = -2.03$, $P < 0.05$) and language ($z = -2.21$, $P < 0.05$) subscale scores and the total score of ABC ($z = -2.37$, $P < 0.05$) decreased. Regarding CARS, visual response ($z = -2.06$, $P < 0.05$), verbal communication ($z = -2.12$, $P < 0.05$) subscale scores, and the total score ($z = -2.52$, $P = 0.01$) decreased significantly after TMS therapy. **Conclusion:** Our study was open label and in terms of sample size should be considered a pilot study. Although the results should be evaluated cautiously, the findings suggest that rTMS might be a safe and useful tool for improving deficits related to ASD in children.

Keywords: *Autism, children, language, prefrontal cortex, repetitive transcranial magnetic stimulation*

Introduction

Deficits in social communication and interaction in addition to restrictive and repetitive patterns of behavior and interests or activities are characteristic symptoms of autism spectrum disorder (ASD).[1] Today, the prevalence of autism is estimated to be 1 in 100 children.[2] As ASD is a very frequent and pervasive developmental disorder affecting multiple areas of cognitive functioning, the burden of the disorder on health-care system and the families is often high.[3] Currently, there is no cure for ASD and apart from behavioral interventions and medications that symptomatically improve aggression and irritability, there is no evidence-based treatment.[4]

Besides medications and behavioral interventions, another possible approach for treatment could be neuromodulation techniques such as transcranial magnetic stimulation (TMS). Neuromodulation methods have the advantage of carrying less adverse effect potential as compared to medical treatment. As compared to behavioral interventions, they are also easier to apply and less time-consuming. However, the main disadvantage of TMS is relative sensitivity to movement as it may be difficult for children to sit still during the session. Second, there is a small but significant risk of epilepsy, especially in people with a previous history. Given a significant proportion of individuals with ASD will have epilepsy, this issue should be assessed carefully. In addition, the suitable lower age limit for the application of TMS is not clearly defined, there have been studies reporting the safety of repetitive TMS in children at 6 years of age.[5] In 2018, there had been 23 eligible reports

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of TMS (four case reports, seven noncontrolled clinical trials, and 12 controlled clinical trials) and meta-analyses revealed a moderately significant impact on stereotypic and social behaviors and the number of errors on executive function measurements and five of these studies reported persistence of the gains for up to 6 months.[6] Another point is that, in the majority of studies, TMS was applied to the dorsolateral prefrontal cortex. The medial prefrontal cortex and motor area were preferred as other application areas. The predominantly applied frequency value was between 0.5 Hz and 1 Hz.[7] Although a temporary and short-term mild headache was stated as the only significant side effect,[7] a recent meta-analysis revealed that the most common adverse effect due to TMS in the pediatric population is facial discomfort and irritability in addition to headache.[8] The prevalence of seizures related to TMS in ASD is limited by a single case and was to a programming error.[9]

Regarding the stimulation site and protocol, there is an inconsistency among previous studies. The dorsolateral prefrontal cortex (DLPFC) either unilateral or bilateral is the most commonly stimulated area, followed by the motor cortex and parietal areas. Both high and low-frequency stimulation protocols were used[10] and some even used theta-burst stimulation (TBS) which is associated with a higher risk of seizures.[11] It is not certain how DLPFC stimulation could be beneficial in ASD, however, speculatively one might say that inhibition of lateral areas related to the task-positive network may enable the activation of task-negative social areas such as the medial prefrontal cortex through reciprocal inhibition. Barahona-Corrêa *et al*.[6] have also noted an increment of the positive effects in the areas of social relations, decline in repetitive behaviors, and improvement in the selective attention process and visual processing areas.

In this pilot study, we aimed to assess the efficacy and applicability of repetitive TMS (rTMS) in a group of children aged 6–19 years. We specifically aimed to record both parent and physician ratings before and after TMS sessions to see if both evaluations would agree.

Materials and Methods

The ethics committee approval has been obtained from Uskudar University Clinical Studies Ethical Commitee. Ethical Permission is approved on October, 27 2017 with the document number of 61351342/2017/20.

Participants

Ten children with ASD have participated in the study. All parents gave verbal and written informed consent and the study protocol was approved by Uskudar University Clinical Studies Ethical Committee. The children with a history of seizures and/or with epileptic seizures detected based on the electroencephalography data obtained in the neurological examination were excluded as well as children with a very high level of hyperactivity who will not tolerate TMS. Inclusion criteria were being diagnosed with ASD by a child psychiatrist or neurologist and being between the ages of 6 and 19 years (M = 12.3, standard deviation (SD) = 3.94) as presented in Table 1. The children who were using medications, vitamins, supplements, or getting behavioral/occupational therapy were allowed to continue the same therapy during the TMS, and no change in the medical treatment was made during the course.

Instruments

Childhood Autism Rating Scale

The Childhood Autism Rating Scale (CARS) is a 15-item behavioral rating scale developed to distinguish individuals with intellectual disability (autism index) without autism from those with autistic symptoms. The CARS test enables autistic individuals to be clinically classified as mild, moderate, and moderate-severe. Each item consists of an evaluation with a half value between one and four points and the scores changes between 15 and 60. Individuals scoring between 15 and 29.5 are far from autism. A score of 30–36.5 indicates mild–moderate autism, and a score of 37–60 indicates severe autism. It is recommended to use 28 points for autistic symptoms and 35 points for

Table 1: Demographic characteristics of participants (*n*=10)

Variable	Value
Age	12.3 (6-19, ±3.94)
Male (%)	100

Age values are presented in years in mean (range and standard deviation)

Table 2: The descriptive statistics and statistical testing for pre–postchange in autistic behavior checklist (*n*=10)

Subtest	Mean±SD	*Z*	*P*
Sensory			
Pretest	8.9±7.5	−1.83	0.07
Posttest	6.2±6.4		
Relating			
Pretest	16.9±10.5	−2.02	0.04
Posttest	13.2±8.3		
Body and object			
Pretest	11.7±9.0	−2.03	0.04
Posttest	8.7±5.8		
Language			
Pretest	16.9±7.6	−2.21	0.03
Posttest	13.2±7.2		
Social and self-help			
Pretest	10.3±5.7	−1.83	0.07
Posttest	8.5±6.2		
Total			
Pretest	64.7±35.4	−2.37	0.02
Posttest	49.8±28.3		

SD: Standard deviation

severe autism. Evaluation can be conducted in the light of classroom evaluation and information received from parents. The Turkish validity and reliability studies of the scale were first performed by Sucuoğlu *et al*.,[12] and the analyzes were expanded by İncekaş Gassaloğlu *et al*.[13]

Autistic Behavior Checklist

The scale was first developed by Krug, Arick, and Almond.[14] It is a test consisting of 57 questions and five subscales: sensory, relating, body and object use, language, and social/self-help. While the lowest score on the scale is 0 and the highest score is 159. Yılmaz-Irmak *et al*.[15] evaluated the validity and reliability of the Autistic Behavior Checklist (ABC) test for our country and determined that it was a usable criterion and determined the cutoff point of the scale as 39. The scale is scored by teacher evaluation. The Cronbach's alpha and Spearman–Brown split-half test reliability coefficients of the scale were found to be. 92. For the reliability of each subtest, the Cronbach's alpha values ranged from 65 (social and self-help) to 82 (relating), and Spearman Brown's two-half test reliability values were similarly 61 (social and self-help) and between 84 (relating).

Transcranial magnetic stimulation application

Each child received 20 sessions of rTMS. The first 10 sessions were given to the left DLPFC and the rest were given to the right DLPFC. In each session, the children received 600 pulses with 90% of the resting motor threshold. We aimed to give TMS 6 days a week but due to interruptions of the schedule, the children received treatment between 23 and 30 days.

Results

All children were between 6 and 19 years of age (M = 12.3, SD = 3.94) and all were male. The means and SDs for the ABC autism checklist are given in Table 2 together with group comparison tests according to the Wilcoxon signed-rank test. According to these results, the relating (z = −2.02, P < 0.05), body and object use (z = −2.03, P < 0.05), and language (z = −2.21, P < 0.05) categories showed a significant decline after TMS treatment. The total score showed also a significant decline (z = −2.37, P < 0.05). Furthermore, CARS results changed significantly in total (z = −2.52, P = 0.01); in addition, visual response (z = −2.06, P < 0.05) and verbal communication (z = −2.12, P < 0.05) scores decreased significantly after TMS therapy [Table 3]. Even if the other subtest evaluations did not change significantly, analyses pointed out a downward trend in adaptation to change (z = −1.807, P = 0.07), listening response (z = −1.890, P < 0.05), activity level (z = −1.84, P = 0.06), and intellectual response (z = −1.89, P = 0.06).

Table 3: Childhood Autism Rating Scale test results (n=10)

Subtest	Mean±SD	*Z*	*P*
Relating to people			
Pretest	2.60±0.91	−1.604	0.11
Posttest	2.25±0.75		
Imitation			
Pretest	2.35±1.03	−1.604	0.11
Posttest	1.90±0.84		
Emptional			
Pretest	2.60±0.94	−1.604	0.11
Posttest	2.10±0.74		
Body use			
Pretest	2.40±0.88	−1.633	0.10
Posttest	2.10±0.74		
Object use			
Pretest	2.20±0.92	−0.921	0.36
Posttest	1.95±0.72		
Adaptation to change			
Pretest	2.15±0.82	−1.807	0.07
Posttest	1.75±0.63		
Visual response			
Pretest	2.20±0.82	−2.060	0.04
Posttest	1.75±0.43		
Listening response			
Pretest	2.20±0.70	−1.890	0.06
Posttest	1.75±0.50		
Taste, smell, and touch response			
Pretest	2.05±1.19	−0.816	0.41
Posttest	1.85±0.88		
Fear or nervousness			
Pretest	2.55±0.80	−1.63	0.10
Posttest	2.15±0.71		
Verbal communication			
Pretest	2.90±0.84	−2.12	0.03
Posttest	2.60±0.88		
Nonverbal communication			
Pretest	2.05±0.93	−1.00	0.32
Posttest	1.95±0.73		
Activity Level			
Pretest	2.4±0.94	−1.84	0.07
Posttest	2.0±0.82		
Level and consistency of intellectual response			
Pretest	2.0±0.62	−1.89	0.06
Posttest	1.75±0.59		
General impressions			
Pretest	2.55±0.80	−1.63	0.10
Posttest	2.30±0.67		
Total			
Pretest	35.2±10.74	−2.52	0.01
Posttest	30.15±7.86		

SD: Standard deviation

Discussion

Our results are consistent with previous studies.[10] In that low-frequency, TMS to bilateral prefrontal areas may be beneficial for children with ASD. According to the results, both parent interviews and clinical evaluations filled in by

the child psychiatrist showed consistent improvement. The subtest analysis reviled two separate evaluations by the parent and the psychiatrist agreed on language abilities. This improvement in our study results corroborates findings in studies examining the effect of TMS on language recovery, especially in aphasias (with and without stroke), revealing the potential of TMS to direct neuroplastic changes that facilitate language recovery.[16-18]

Another important aspect of the result of the study is that we applied rTMS to a relatively younger population as compared to previous TMS studies and none of the children left the study due to side effects. On the other hand, it is worth mentioning that we excluded children with a high level of hyperactivity or aggression. For those children who may not tolerate regular TMS, shorter treatments with theta-burst-type stimulation may be suitable. Looking at the recommendations in the literature, for instance,[19] conducted an open-label study suggesting that intermittent TBS (iTBS) would modulate synaptic plasticity more efficiently than TMS and could be a promising modality for neuropsychiatric disorders such as ASD. Researchers have revealed results that indicate improvement in some cognitive functions and proposed the necessity of further controlled studies of iTBS.

The most important shortcoming of our study is that our sample size was relatively small. However, it should also be kept in mind that our sample size was comparable to previous TMS treatment studies with ASD children. Another limitation is the lack of a control group. A sham-controlled double-blind treatment study might yield more reliable results in terms of the effectivity of TMS in ASD. Therefore, with continuity and optimal stimulation of what is reflected in the research, you can keep the numbers and duration.

Conclusion

This study, evaluating rTMS treatment for children with ASD in the mean age of 12 years, has revealed that both total score and and three subtests (the relating, body and object use and language categories) of ABC test showed significant decline after TMS treatment. Also, significant change in total scores of CARS, visual response and verbal communication subtest scores decreased significantly after rTMS. Other subtests results were not significant, whereas non-significant decrease in adaptation to change, listening response, activity level, and intellectual response was detected.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Nevzat Tarhan (20%): Organized the research and contributed with comments on manuscript organization
- Muammer Aydoğdu: (20%): data collection and analyses
- Yelda İbadi (20%): Contributed on manuscript organization and write-up.
- Emel Sarı Gokten (20%): Design the research, data collection and analyses
- Barış Metin (20%): Design the research, contributed with comments on manuscript organization and write-up.

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