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Case Series

Personalized rTMS in Pediatric Patients with Autism: A Case Series Exploring Therapeutic Outcomes

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Received: February 12, 2025; **Published:** March 13, 2025

Abstract

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental condition which has been previously linked to disruptions in the excitatory and inhibitory (E/I) balance of the brain. Personalized repetitive transcranial magnetic stimulation (PrTMS®) guided by spectral EEG has gained traction as a novel treatment option targeting these neurophysiological disturbances. This case series evaluates the therapeutic outcomes of PrTMS® in three pediatric patients with ASD. Over six weeks, participants received daily PrTMS® sessions, with weekly adjustments to treatment protocols informed by their spectral EEG findings and psychometric assessments. On average, CARS scores decreased by 7.5 points across all patients by the end of treatment, indicating improvements in autism-related symptoms. Patients 1 and 2 exhibited a 9-point reduction in ADHD symptoms, as measured by the NICHQ Vanderbilt Assessment Scale. These results align with prior research, suggesting that PrTMS® may effectively regulate cortical activity and restore E/I balance, contributing to clinical improvements in ASD. Despite the small sample size, this study underscores the potential of PrTMS® as a targeted intervention for ASD, meriting further exploration in studies of larger scales.

Keywords: *Personalized Repetitive Transcranial Magnetic Stimulation (PrTMS®); Repetitive Transcranial Magnetic Stimulation (rTMS); Neuromodulation; Autism; Autism Spectrum Disorder; Spectral EEG; Spectral Electroencephalogram; CARS (Childhood Autism Rating Scale); NICHQ Vanderbilt Assessment Scale; Alpha Brainwave Activity*

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition comprising challenges in social communication, repetitive behaviors, and sensory processing [1]. Individuals with autism may also present with co-occurring conditions, such as attention-deficit/hyperactivity disorder (ADHD) [2]. Furthermore, children with autism have been found to frequently present with anxiety-related disorders, exacerbating behavioral issues such as anger outbursts, which lead to avoidance behaviors and functional impairment. [3]. The role of altered levels of neurotransmitters in the manifestation of symptoms of autism, has previously been explored through neuroimaging techniques [1]. Dysregulation of dopamine (DA) within the mesolimbic reward pathway has been explored as a possible intersection for the various genetic, epigenetic, and environmental influences linked to ASD. Disruptions in DA signaling are believed to give rise to challenges in social interaction, cognitive function, and motivation associated with ASD [4]. Furthermore, it has been suggested that an imbalance between excitatory and inhibitory (E/I) signaling in the brain may contribute to the neurobiological basis of these symptoms [1].

Studies using repetitive transcranial magnetic stimulation (rTMS) have provided additional insights into cortical E/I processes in autism [1]. In combination with EEG, rTMS has been found to possess potential in identifying key biomarkers in various neuropsychiatric disorders [5]. The study of these changes in neural activity has previously revealed potential deficits in cortical inhibition in individuals with autism [6]. rTMS has additionally emerged as a therapeutic tool for regulating cortical excitability and restoring E/I balance [1], as well as improving frontal-posterior feedback connectivity [6]. Previous studies have suggested that rTMS may play an effective role in improving cognitive outcomes in youth and young adults on the autism spectrum [7]. It is typically a well-tolerated treatment modality, with mild and temporary side effects like headaches or scalp discomfort at the treatment site [8], while more severe but rare side effects such as seizures carry an overall risk of less than 1% [9].

Personalized rTMS (PrTMS®), which utilizes individual neurophysiological data, has been seen to hold promise as a therapeutic strategy to address the heterogeneous clinical manifestations of ASD. This modality employs spectral electroencephalogram (EEG) and psychometric assessment data to generate customized treatment protocols for each patient using the PeakLogic™ software, aimed at maximizing therapeutic outcomes [10,11]. PrTMS® has demonstrated encouraging results in addressing conditions including autism, PTSD, concussion, sleep disturbances, anxiety, and depression [12-16].

This case series further expands on these insights, investigating the clinical outcomes of PrTMS® in three pediatric patients with ASD.

Case Presentations

Case 1

A 9-year-old male previously diagnosed with autism and ADHD presented with decreased verbal communication, social interaction, and focus in class, along with episodes of inappropriate laughter and temper tantrums. Prenatal history included first-trimester bleeding managed with medication, preterm delivery via caesarean section for oligohydramnios, and reduced fetal movements. Postnatal milestones were delayed, as evidenced by rolling over at 4 months, walking without support by 13 months, and running at 22 months. Speech delay was evident at 3 years of age, prompting speech therapy, with limited word acquisition by 4 years of age. At 8 years of age, he could write partial alphabets and numbers, dress himself with minimal assistance, and independently manage feeding and toileting. Despite adequate behavioural interventions, his progress was impacted by impaired adaptive functioning, below-average intellectual functioning, sensory insensitivities, and anxiety, which hindered spontaneous learning. At the time of presentation, the patient's sleep and bowel habits were reportedly normal, and his vaccination schedule was up to date.

Case 2

A 12-year-old male previously diagnosed with autism and ADHD presented with delayed developmental milestones from the age of 2, intellectual disability, hand fidgeting, repetitive behaviors, and inappropriate laughter and self-talking. He was born at term via normal delivery, weighing 3.2 kg (7.06 lb) with normal APGAR scores. Early milestones were appropriate until 2 years of age, but pincer grasp was delayed till 4 years of age and two-word speech was achieved at 5 years of age. The patient started play school at 2 years of age and

was attending regular school at the time of presentation. He had been receiving occupational and speech therapy since the age of 2. There were no reported sleep or bowel disturbances, and the patient's vaccination schedule was up to date.

Case 3

A 16-year-old male with a prior diagnosis of autism presented with reduced socialization and difficulty comprehending information from reading or listening. He was born via lower-segment caesarean section, weighing 2.5 kg (5.5 lb), and did not cry spontaneously at birth. Milestones included walking by 1 year and speaking disyllabic words by 1.5 years, with normal fine motor skills. The patient displayed selective responsiveness early on, engaging socially only with his parents and selectively concentrating on tasks of interest. He also exhibited a repetitive speech pattern and experienced anxiety that frequently led to avoidance behaviours. In response to distressing situations, he engaged in involuntary vocalizations as a coping mechanism. At the time of presentation, the patient was enrolled in high school and had recently completed his 10th-grade exit examination. No sleep or bowel disturbances were reported at the time of presentation.

Materials and Methods

Study participants

Participants included patients under 18 years of age with an initial clinical diagnosis of autism spectrum disorder. Treatments were administered five days a week over a six-week period at a clinical practice in Chennai, India. Written informed consent was obtained from the parent or legal guardian of each participant prior to the study.

Spectral EEG data

Spectral EEG recordings were performed weekly using a CGX high-impedance dry electrode headset. Electrode placement followed the International 10-20 system.

Psychometric questionnaires

Treatment response to PrTMS® was evaluated weekly using psychometric questionnaires. Childhood Autism Rating Scale (CARS) was utilized to assess autism symptoms in all participants, while National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale was administered to participants 1 and 2 to assess ADHD symptoms throughout the treatment period. Parents or legal guardians of the patients completed the evaluations for both assessment scales, providing insight into symptom changes over the course of treatment.

Personalized repetitive transcranial magnetic stimulation (PrTMS®) treatment

PrTMS® was delivered by a trained neurotechnologist using PeakLogic® software integrated into the Apollo TMS Therapy System. Stimulation targeted specific scalp locations, including FPz (Prefrontal Zero), Fz (Frontal Zero), Cz (Central Zero), F3 (Left Dorsolateral Prefrontal Cortex), and F4 (Right Dorsolateral Prefrontal Cortex). Weekly adjustments to stimulus frequency and amplitude were guided by a computerized algorithm based on spectral EEG data and standardized psychometric scores. Unlike conventional rTMS, PrTMS® does not require motor threshold determination, simplifying the procedure and reducing patient burden. The magnetic stimulation was delivered at an individually tailored intensity. Sessions lasted approximately 30 minutes daily, 5 days each week, over a 6-week period.

Results

Patient 1

Psychometric Questionnaire	Week 1	Week 2	Week 3	Week 5	Week 6
CARS	40	39.5	38.5	33	32
NICHQ Vanderbilt Assessment Scale	33	35	32	26	24

Table 1

Patient 2

Psychometric Questionnaire	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
CARS	33.5	33.5	31	29	28	27
NICHQ Vanderbilt Assessment Scale	27	24	25	24	19	18

Table 2

Patient 3

Psychometric Questionnaire	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
CARS	31	31	30	24.5	24.5	23

Table 3

Discussion

It has been hypothesized that PrTMS® guided by spectral EEG may enhance treatment outcomes for individuals with autism spectrum disorder by addressing its neurophysiological underpinnings. The hypothesis suggests that ASD involves a disruption in the brain's excitation-inhibition balance, leading to dysregulated alpha-band EEG oscillations and impaired reward system functioning, thus contributing to psychosocial deficits. By targeting these imbalances, it has been suggested that PRTMS® could restore alpha oscillation synchronization, and improve brain reward signaling. PRTMS® utilizes personalized parameters tailored to each individual's EEG profile and psychometric evaluations. This results in a customized approach with continuous updates to the treatment protocol throughout the treatment course [10].

The mechanism through which PRTMS® may improve treatment outcomes in ASD can be demonstrated by findings from a clinical pilot study by Makale., *et al*. which evaluated the effects of PRTMS® in 123 individuals with ASD undergoing Applied Behavior Analysis (ABA) therapy. The PRTMS® protocol involved low-intensity TMS pulses, with continuously updated treatment algorithms that were informed by spectral EEG data and psychometric assessments. It was reported that 44% of participants experienced a reduction in ASD scale scores to below diagnostic thresholds, with no adverse effects reported during the course of treatment. In responders (i.e. participants whose scores decreased below a specific cutoff score), it was also found that spectral EEG regression lines flattened, reflecting a more balanced excitatory-inhibitory ratio. Older participants showed an increase in alpha peak frequency, correlating with improved non-verbal cognitive function [11].

The CARS scores of our three participants showed an observed average reduction of 7.5 points by the end of the treatment period (scores shown in table 1-3). Patients 1 and 2, who were also assessed throughout the treatment period using the NICHQ Vanderbilt Assessment Scale, demonstrated an average score reduction of 9 points by the end of treatment (scores shown in table 1 and 2). The mean decrease in patient scores on both assessment scales correlates with an improvement in clinical symptomatology. This is comparable to the results seen with 70 participants in the study by Makale., *et al*. who were administered the CARS assessment [11]. They demonstrated a similar decrease in the average score from 36 before PRTMS® to 33 at Week 4, and 30 at Week 6. This group comprised 55 males and 15 females, with an average age of 13 and a median age of 11 years of age. 26 participants in this group were classified as responders who exhibited significant improvements, with their average CARS scores dropping from 35 at baseline to 29 at Week 4, and further to 25 at Week 6.

Although this case series is limited by its small sample size, we believe it provides valuable insights into the potential of PrTMS® as a treatment for autism spectrum disorder. An additional limitation is the lack of CARS and NICHQ Vanderbilt Assessment Scale scores for patient 1 during the fourth week of treatment, due to technical issues with the software that prevented the data from being saved.

However, the observed reductions in psychometric assessment scores among our participants align with the findings of previous studies of a larger scale, supporting the hypothesis that PrTMS® can effectively target the neurophysiological imbalances associated with ASD. These findings suggest that a personalized, EEG-informed approach to neuromodulation may offer promise in improving clinical outcomes in individuals with autism, warranting further investigation in larger, controlled studies.

Conclusion

Personalized neuromodulation presents a novel and individualized approach to autism treatment, with the potential to greatly enhance clinical outcomes. The improvements in patient CARS assessment scores are indicative of the role of PrTMS® in improving autism-related symptomatology. Additionally, the average reduction in ADHD symptoms as measured by the NICHQ Vanderbilt Assessment Scale, further underscores the therapeutic significance of PrTMS® in addressing co-occurring conditions often present in ASD. PrTMS® may play a substantial role in restoring disrupted excitatory-inhibitory balance in the brain that underlies many of the challenges associated with autism. In view of these findings, further research involving larger, randomized controlled trials is essential to better understand the long-term role of PrTMS® in improving the quality of life of individuals on the autism spectrum.

Author Contributions

The original draft of this manuscript was written by K.M, L.S, S.K.K, C.V, S.M, S.K, and K.S. Review and additional editing of the manuscript were conducted by K.T.M, K.B, K.U.L, R.D.B, M.S.G, and K.S.

Conflict of Interest Statement

There are no conflicts of interest declared by the authors regarding publication of this paper. This manuscript has been read and approved by all authors.

Declaration of Patient Consent

The authors confirm that written informed consent has been obtained from the study participants for publication of this research.

Acknowledgements

K.B is the NIH recipient of R41 MD012318/ MD/NIMHD NIH HHS/United States. R.D.B. is supported by NIH grant R01NS073884. The funding sources had no role in the design, data collection, analysis, or preparation of this manuscript.

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Volume 17 Issue 4 April 2025
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