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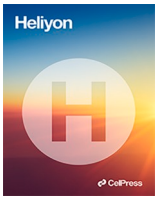

Research article

Assessing the impact of repetitive transcranial magnetic stimulation on effective connectivity in autism spectrum disorder: An initial exploration using TMS-EEG analysis

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ABSTRACT

Initial indications propose that repetitive transcranial magnetic stimulation (rTMS) could mitigate clinical manifestations in patients with autism spectrum disorder (ASD). Nevertheless, the precise mechanisms responsible for these therapeutic and behavioral outcomes remain elusive. We examined alterations in effective connectivity induced by rTMS using concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) in children with ASD. TMS-EEG data were acquired from 12 children diagnosed with ASD both before and following rTMS treatment. The rTMS intervention regimen included delivering 5-s trains at a frequency of 15 Hz, with 10-min intervals between trains, targeting the left parietal lobe. This was conducted on each consecutive weekday over 3 weeks, totaling 15 sessions. The dynamic EEG network analysis revealed that following the rTMS intervention, long-range feedback connections within the brains of ASD patients were strengthened (e.g., frontal to parietal regions, frontal to occipital regions, and frontal to posterior temporal regions), and short-range connections were weakened (e.g., between the bilateral occipital regions, and between the occipital and posterior temporal regions). In alignment with alterations in network connectivity, there was a corresponding amelioration in fundamental ASD symptoms, as assessed through clinical scales post-treatment. According to our findings, people with ASD may have increased long-range frontal-posterior feedback connection on application of rTMS to the parietal lobe.

1. Introduction

Autism spectrum disorder (ASD) is a developmental disability defined by persistent deficits in social interaction and communication, together with narrow interests and repetitive actions [1]. A recent report from the US Centers for Disease Control and Prevention, about one in 44 eight-year-old have an ASD diagnosis [2]. However, biomedical treatments aimed at addressing the core symptoms of ASD have notable limitations. Focusing on the underlying mechanisms of ASD may facilitate the development of new forms of treatment.

Atypicalities in brain connectivity have been recognized as the core pathologies of ASD [3,4]. In neurobiology, ASD is seen as a breakdown in neural circuit integration rather than a localized impairment. Type of connectivity dysfunction in autism remains a

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source of debate, with experts disputing whether it is under- or over-connected [5–7]. Recent evidence suggests both hypotheses may be valid depending on the directionality of connectivity. In ASD, functional connectivity increases in the feed-forward direction while decreasing in feedback (e.g., frontal-parietal circuit) [8–10]. This pattern of increased bottom-up processing and weak top-down signaling aligns with ASD severity.

Effective connectivity, which addresses the directionality of information flow or the influence of one region on another, provides a multilevel characterization of neural communication in autism [11]. Transcranial magnetic stimulation (TMS) and EEG co-registration (TMS-EEG) offer valuable insights into effective connectivity. This method involves evaluating the brain's electrical activity by EEG following a short and non-intrusive brain stimulation utilizing TMS. The experimental assessment of successful connectivity is facilitated by the fact that TMS activation in the specific location spreads to functionally and anatomically associated regions [12,13]. TMS-EEG offers precise measurements of efficient connectivity with high temporal precision by analyzing the network's response to the stimulation of one of its nodes. It accomplishes this by sequentially stimulating the cortex and assessing the ensuing activity in the cortex at both regional and global network levels [14].

In recent years, the time-varying directed EEG network revealed by TMS-EEG has become particularly suitable for studying dynamic brain activities and patterns of instantaneous causality within neural networks. Although numerous parametric methods exist for constructing time-varying directed EEG networks, the most widely used method is the adaptive directed transfer function (ADTF) because of its good performance in interpretation and accurate capture of the time-variant causality between signals [15,16].

In specialized, interconnected cortical modules, repetitive transcranial magnetic stimulation (rTMS) with different stimulation patterns can cause functional reorganization and change cortical excitability [17]. A substantial body of evidence suggests that rTMS may represent a promising therapeutic approach in addressing the core manifestations of ASD [18–20]. However, the precise mechanism responsible for this clinical improvement remains shrouded in ambiguity. Previous studies have shown that rTMS can cause measurable alterations in cortical coherence and synchronization [21,22]. ASD symptoms may be lessened by high-frequency rTMS that target the parietal cortex and modify the abnormal functional connectivity of the resting-state network [23]. Nevertheless, the majority of inquiries have predominantly centered on examining functional connectivity, leaving us with limited insights into the repercussions of rTMS on effective connections.

In order to examine this issue, the current study utilized ADTF analysis of TMS-EEG to create time-varying directed networks for all the children that were recruited. Our objective was to examine the modified changes in effective connectivity following rTMS treatment in children with ASD.

2. Methods

2.1. Participant

Twelve children with ASD (9 boys, age 7.17 ± 3.10 years) were enrolled. Neuropediatricians used DSM-5 criteria to validate the clinical diagnosis of ASD in children. The exclusion criteria were the presence of tuberous sclerosis and Fragile-X syndrome, past seizure disorders or serious head injuries, metal implants, medication with anticonvulsant or antipsychotic drugs, or a history of important medical or neurological disorders. The Childhood Autism Rating Scale (CARS) was utilized to evaluate the clinical severity of ASD symptoms [24]. Ethical approval was provided by the Xuanwu Hospital ethics committee (Approval No. LYS2019127), and before participation, informed consent was provided by the participants' parents. Table 1 summarized the participant demographics and CARS scores.

2.2. Experimental procedures

TMS-EEG data were initially gathered from children with ASD before rTMS therapy, denoted as *pre*-rTMS. Subsequently, all children underwent a three-week regimen of rTMS treatment. After the rTMS treatment, TMS-EEG data were collected again using the

Table 1
Participant demographics and CARS scores.

Participant number	Sex	Age (years)	CARS (scores)
1	Male	4	32
2	Male	5	30
3	Male	4	30
4	Male	13	40
5	Female	7	34
6	Male	13	30.5
7	Male	7	34
8	Male	9	31
9	Female	7	35.5
10	Female	5	32
11	Male	5	33
12	Male	7	38

Note: CARS, Childhood Autism Rating Scale (CARS).
Higher scale scores indicate higher severity of symptoms.

same criteria as before the rTMS treatment. This data is referred to as *post*-rTMS (Fig. 1a).

The efficacy of the treatment was evaluated employing the Social Responsiveness Scale (SRS) [25], the Repetitive Behavior Scale-Revised (RBS-R) [26], and the Autism Treatment Evaluation Checklist (ATEC) [27]. The ATEC consists of four subscales: Scale I focuses on speech, language, and communication; Scale II measures sociability; Scale III assesses sensory and cognitive awareness; and Scale IV evaluates health, physical abilities, and conduct [27]. These evaluations were administered both immediately before and following the rTMS intervention.

2.3. The rTMS stimulation parameters

We applied rTMS employing a 70-mm figure-of-eight coil connected to a Magstim Rapid 2 stimulator manufactured by Magstim Company Ltd. UK. The stimulation was accurately administered to the left parietal brain, with a specific emphasis on electrode P3 on the EEG cap. The parietal cortex was selected as a stimulating region in the present study for the following reasons: First, it plays a critical role in information navigation, spatial perception, and integration. It is also implicated in sensory-motor processing, attention, and a variety of psychiatric diseases, including ASD [28]. Second, relative to non-ASD controls, individuals with ASD show cerebral hypoperfusion in the parietal cortex. Additionally, there is a connection between ASD symptomatology and cerebral hypoperfusion [29]. Third, according to Ye et al. [30], there is an aberrant connection between the parietal cortex and extensive areas in ASD. According to our hypothesis, parietal lobe high-frequency rTMS could enhance cortical excitability and cerebral blood flow, promoting connections between the parietal cortex and other parts of the brain. Furthermore, prior research has shown that high-frequency rTMS across the left parietal cortex may help children with ASD with their speech and social deficits [19,23]. The therapeutic regimen consisted of a series of five 5-s trains delivered at a frequency of 15 Hz, with 10-min intervals between each train. For 3 weeks, this treatment was administered every day, Monday until Friday, for an overall of 15 treatment sessions in one course (Fig. 1a).

The lowest TMS intensity resulting in motor-evoked potentials of at least 50 μV in 50 % of trials in the first dorsal interosseous

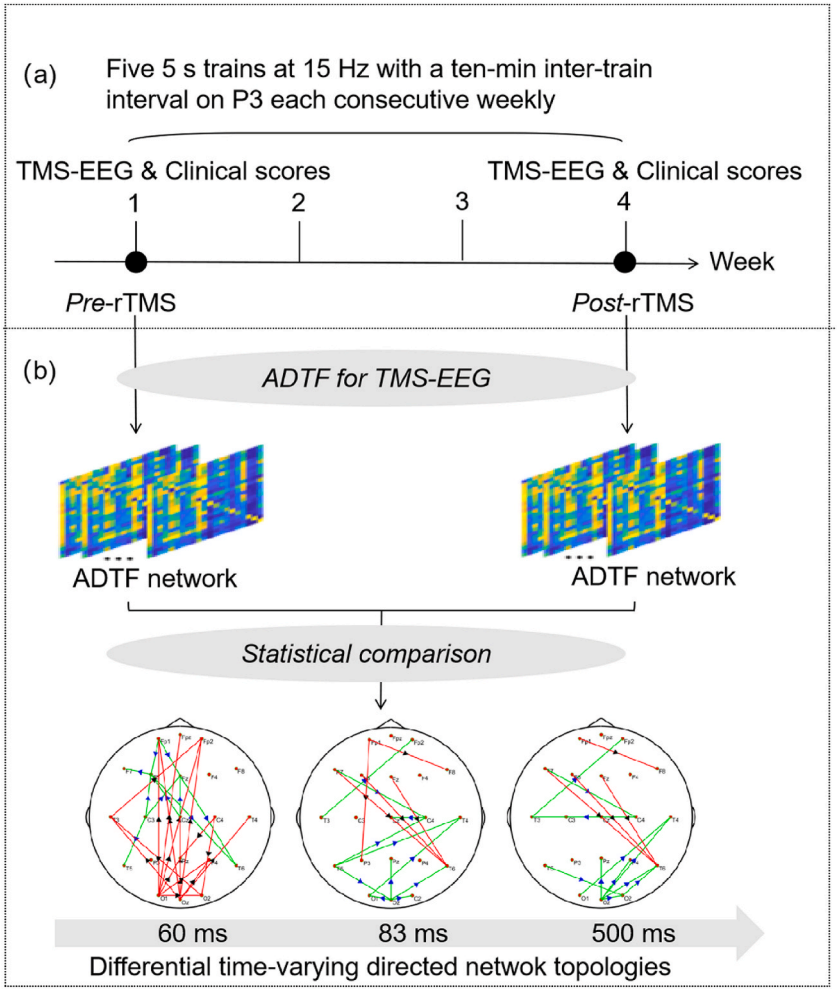

Fig. 1. Approaches for analysis. (a) The steps involved in the rTMS experiment. (b) The investigation of effective connectivity.

muscle was defined as the resting motor threshold (RMT). Completing the process would typically require 30 min. Participants often face challenges maintaining their positions for this duration during RMT measurements due to behavioral problems, intolerance to touch, and tactile hypersensitivity in ASD. Because the majority of ASD children are unable to participate in motor threshold examinations, we previously described RMT evaluations in children diagnosed with Tourette syndrome (aged 7–13 years) and children diagnosed with attention deficit hyperactivity disorder (aged 8–13 years) within our research facility. These RMT values typically fell within the 40 %–50 % range. As a result, we set a constant 50 % of the stimulator output as the stimulation intensity.

2.4. TMS-EEG data acquisition

We procured TMS-EEG data for 20 min, utilizing a magnetic field-compatible EEG amplifier (with a sample rate of 1024 Hz, sourced from Beijing Yunshen Ltd., Beijing, China). The EEG cap, consisting of 32 electrodes, was tailored for TMS compatibility and positioned following the 10–20 montage. To ensure optimal data quality, we diligently maintained electrode impedances at levels below 5 kΩ. In our setup, the AFz channel functioned as the reference point, with electrodes placed at the nasal tip serving as the ground. A total of 200 single-pulse TMS (sTMS) impulses were administered to the left parietal lobe, especially targeting electrode P3 on the EEG cap. The strength of the stimulation was 50 % of the output of the stimulator. The stimulation target and intensity were consistent with the rTMS treatment protocol. Each instance of the sTMS application featured a 4-s interval to minimize the cumulative effects of TMS, with concurrent EEG recordings documented. During the data collection process, all patients were instructed to maintain a seated, motionless posture with closed eyes. Additionally, they were provided with earplugs to mitigate any potential disturbances arising from ambient noise or coil discharges.

2.5. TMS-EEG data analysis

The methodology employed to scrutinize disparities in the network structures of effective connectivity before and after treating individuals with ASD is succinctly illustrated in Fig. 1. This encompasses the specifics of the rTMS experiments (Fig. 1a) and the subsequent examination of effective connectivity (Fig. 1b). Further elaboration on the associated sub-processes is provided below. The analysis of TMS-EEG data, encompassing preprocessing and the examination of time-varying directed networks, was executed utilizing MATLAB (R2015b, The Mathworks, USA).

2.5.1. The preprocessing of the EEG data

The initial data preparation steps encompassed the implementation of a bandpass filter ranging from 0.5 to 30 Hz, along with the segmentation of the data. Disturbances induced by sTMS served as the markers for stimulation events. For each event marker, the precise moment coinciding with the pinnacle of the marker was designated as the temporal reference point '0'. Subsequently, data corresponding to the 0.5s interval preceding this reference point (established as the baseline) and the subsequent 2 s were extracted. Given the inevitable artifacts introduced by TMS in EEG signals, our primary focus resided within the timeframe of 60–1400 ms following sTMS stimulation.

2.5.2. Time-varying directed network analysis

The process of analyzing a time-varying network entails a series of procedural stages aimed at creating a reliable network capable of encapsulating the attributes of effective connections. Initially, for the sake of managing computational complexity, the data segments were subjected to downsampling, ultimately arriving at a rate of 128 Hz for the final analysis. We next calculated the ADTF matrix and set out the development of a tv-MVAAR (time-varying multivariate adaptive autoregressive) model.

2.5.2.1. The tv-MVAAR model. For each artifact-free segment, the tv-MVAAR framework can be expressed as follows:

$$X(t) = \sum_{i=1}^{p} A(i,t)X(t-1) + E(t) \tag{1}$$

The tv-MVAAR model's determined coefficients are stored in the matrix $A(i,t)$ in Equation (1), where $X(t)$ is the data vector of the EEG signal at time t, $E(t)$ is a vector of multivariate independent white noise, and the Kalman filter algorithm is used for calculating the model's parameters. The parameter p represents the order of the model, which is determined automatically using the Akaike Information Criterion (AIC) within the range of 2–20.

$$AIC(p) = \ln[\det(\chi)] + 2M^2 p/N \tag{2}$$

Within Equation (2), M stands for the quantity of electrodes, p signifies the most suitable model order, N indicates the count of time points within each time sequence, and χ represents the covariance matrix affiliated with it.

2.5.2.2. Adaptive directed transfer function. Parameters $A(f,t)$ and $H(f,t)$ in the frequency domain are as follows:

$$A(f,t) = \sum_{k=0}^{p} A_k(t) e^{-j2\pi f \triangle tk} \tag{3}$$

$$A(f,t)X(f,t) = E(f,t) \tag{4}$$

$$X(f,t) = A^{-1}(f,t)E(f,t) = H(f,t)E(f,t) \tag{5}$$

A_k in Equation (3) refers to the matrix that contains the coefficients of the tv-MVAAR model. *X(f,t)* and *E(f,t)* in Equation (4) and Equation (5) represent the Fourier transformations of *X(t)* and *E(t)* in the frequency domain, respectively.

In the context of normalized ADTF, Equation (6) outlines the representation of directed flow from the *j*th to the *i*th node. Equation (7) precisely defines the eventual integrated ADTF within the frequency range of interest.

$$\gamma_{ij}^2(f,t) = \frac{\left|H_{ij}(f,t)\right|^2}{\sum_{m=1}^{n}\left|H_{im}(f,t)\right|^2} \tag{6}$$

$$Q_{ij}^2(t) = \frac{\sum_{k=f_1}^{f_2}\gamma_{ij}^2(k,t)}{f_2 - f_1} \tag{7}$$

The normalized total information outflow from the *j*th node can be calculated using Equation (8):

$$Q_j^2(t) = \frac{\sum_{k=1}^{n} Q_{kj}^2(t)}{n-1}, for\ k \neq j \tag{8}$$

In this context, *n* represents the overall count of nodes. For every node (*n*) at each *t* (time point), a directional connection (*i* to *j*) was depicted. Equation (8) enabled us to deduce an outflow, illustrating the temporal changes of each node over various time points.

2.5.3. Statistical analysis

After construction of the dynamic-directed EEG network, we used a paired sample *t*-test to analyze differences in brain connections between children with ASD prior to and following rTMS therapy. For maximum accuracy, we applied false discovery rate (FDR) correction.

3. Results

3.1. Effectiveness of rTMS in clinical settings

Twelve children with ASD successfully underwent the rTMS intervention course without encountering any severe adverse events. Our attention then turned to the evaluation of clinical outcomes using specific assessment scales: ATEC, SRS, and RBS-R. The data presented in Table 2 revealed noteworthy reductions in total scores across these three scales following the completion of rTMS course. Furthermore, among the ATEC subscales, 3 out of 4 (including language, social interactions, and sensory-cognitive awareness) displayed a notable decline ($p < 0.05$).

3.2. Pre- and post-rTMS configuration differences in time-varying directed EEG networks

Alterations in the time-varying directed network exhibited notable distinctions before and after the rTMS intervention among ASD patients (Fig. 2). Compared with the network patterns before rTMS, between 60 ms and 83 ms after single-pulse TMS of the left parietal lobe, a substantial rise in information transmission from the bilateral occipital regions to the bilateral frontal regions was evident ($p < 0.05$, FDR corrected). Simultaneously, there was a significant decrease in the connections between the bilateral frontal lobes and the

Table 2
Clinical scale scores obtained from each evaluation stage.

	Pre-rTMS	*Post*-rTMS
ATEC total score	60.92 ± 11.74	46.17 ± 13.64[a]
ATEC subscale score		
ATEC-language scale	9.17 ± 4.80	6.08 ± 3.0[a]
ATEC-social scale	19.25 ± 4.45	13.08 ± 5.63[a]
ATEC-sensory and cognitive awareness scale	14.83 ± 4.93	10.75 ± 5.40[a]
ATEC-health and behavioral problems scale	17.67 ± 5.82	15.92 ± 4.46
SRS	100.67 ± 20.89	85.58 ± 21.07[a]
RBS-R	23.17 ± 11.26	17.08 ± 11.52[a]

Notes.
Decreased scores indicate diminished impairments.
[a] Statistically distinguishable from the *pre*-rTMS phase based on paired-sample *t*-test ($p < 0.05$).

centrotemporal region ($p < 0.05$, FDR corrected). Between 83 ms and 1400 ms, there was a considerable increase in the effective connections from the frontal regions to the parietal regions, particularly the left frontal-parietal connection, and the right posterior temporal region, compared to the connections observed before the onset of ASDs ($p < 0.05$, FDR corrected). Connections among the posterior brain regions (such as connections between bilateral occipital regions and between the occipital and posterior temporal regions) significantly decreased ($p < 0.05$, FDR corrected).

In summary, the time-varying EEG network revealed that, after rTMS intervention, long-range feedback brain connections in patients with ASD were strengthened (e.g., frontal to parietal regions, frontal to occipital regions, and frontal to posterior temporal regions) and short-range connections were weakened (such as between the bilateral occipital regions, and between the occipital and posterior temporal regions).

4. Discussion

Here, changes in the dynamic-directed network of individuals with ASD following rTMS therapy were explored. Our results suggest that the administration of high-frequency rTMS to the parietal lobe has the potential to strengthen long-range feedback connections within the brain while simultaneously diminishing short-range connections in posterior brain regions. These shifts in the dynamic network architecture may align with observed improvement in core ASD symptoms, as assessed through SRS, RBS-R, and ATEC, after rTMS intervention.

ASD is a multifaceted condition characterized by various causal factors, comorbid conditions, and significant variation in symptoms among individuals. Additionally, the neurobiological effect of rTMS may depend on the individual characteristics of the stimulated brain [31]. Thus, not all children with ASD derive equal benefits from the same rTMS paradigm, emphasizing the need for customized and tailored therapeutic approaches. We previously showed that using high-frequency rTMS on the parietal cortex can improve long-distance connectivity in the resting-state network of individuals with ASD. This stimulation is particularly effective in enhancing connections between the frontal and parietal regions, as well as the frontal and occipital regions, within and between the brain hemispheres [23]. This pilot study indicated that the identical rTMS intervention may enhance long-range front-posterior feedback connectivity in a time-varying network. These findings potentially pave the way for a connectivity-based targeting strategy to identify ideal candidates for left parietal lobe TMS interventions, particularly benefiting individuals with underconnectivity between frontal and posterior regions.

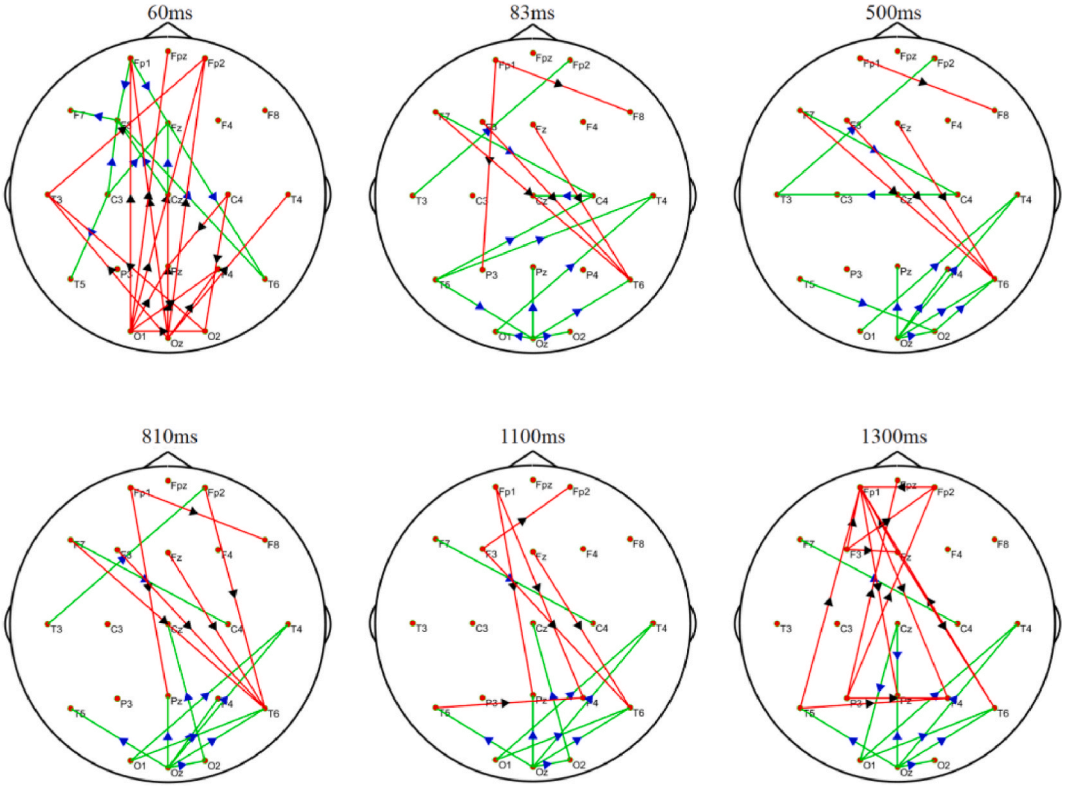

Fig. 2. The disparity in the dynamic EEG network configurations prior to and following rTMS in patients diagnosed with ASD. Time (in milliseconds): following single-pulse TMS. Red lines: stronger connections in *post*-rTMS ASDs than in *pre*-rTMS. Green lines: reduced connections in *post*-rTMS ASDs in comparison to *pre*-rTMS. Black arrows: depict the direction of information transmission. Blue arrows: depict the direction of information transmission.

Extensive evidence indicates that individuals with ASD typically exhibit a pattern of underconnectivity across the brain, potentially alongside localized overconnectivity [32,33]. Investigations employing functional magnetic resonance imaging (fMRI) and EEG have further substantiated diminished connectivity, particularly in frontoparietal and fronto-occipital regions, within ASD individuals [34–37]. The frontal lobe, involved in higher-order cognition and language processing, as well as social and emotional faculties, is of paramount importance [38]. Impairments in top-down signaling from the frontal to posterior regions can result in deficits in tasks heavily reliant on frontal involvement, potentially underpinning the observed challenges in cognitive, social, and linguistic processing experienced by individuals with ASD. This study analyzed the dynamic-directed EEG network and found that rTMS activated the frontal cortex, resulting in increased connection with posterior brain regions, particularly the occipital and parietal regions. RTMS may augment long-range feedback connections, which could play a role in the observed clinical improvement.

In individuals diagnosed with ASD, local overconnectivity, arising from radial cytoarchitectural irregularities, typically manifests in several brain regions, including the frontal lobes [39]. Comparatively, this local overconnectivity assumes the appearance of a peninsula, set apart and with restricted access to the broader brain network. Consequently, long-distance underconnectivity ensues as a consequence. This suggests that the brain may employ areas with more accessible connections, such as nearby regions, to compensate for the irregular connectivity patterns [40]. The notion of an excessively connected peninsula might extend beyond the confines of the prefrontal cortex, as heightened connectivity in posterior regions within individuals with autism might result in posterior autonomy [3]. An intriguing question to ponder is whether the overconnectivity, both frontal and posterior, is a result or a causative factor of the frontal-posterior underconnectivity. We found that, alongside enhanced long-range connectivity, there was a concurrent attenuation in short-range connections within posterior regions after rTMS treatment, potentially aligning with the compensatory mechanism of the brain network.

Several limitations should be noted in the present study. It should be noted that this is a preliminary investigation, which means that there is a need to validate the results with a larger patient sample due to the low sample size. Second, the veracity of the rTMS intervention's results raises concerns because a control group with sham stimulation was not included. Nevertheless, the alterations observed in the functional network configuration after rTMS may partially mitigate concerns of a placebo effect. Subsequent research endeavors should encompass larger populations, meticulously chosen neurobiological targets and personalized assessments to delineate precise therapeutic protocols and optimize clinical outcomes.

5. Conclusion

In sum, our results suggest that the application of high-frequency rTMS on the parietal lobe has the potential to strengthen long-range frontal-posterior feedback connectivity in individuals with ASD.

Ethical approval

The Institutional Review Board of Xuanwu Hospital of Capital Medical University (LYS2019127) approved this study in December 2019.

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Data availability statement

The corresponding author can provide all the data from this work upon a reasonable request.

CRediT authorship contribution statement

Yingxue Yang: Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Penghui Song:** Methodology, Formal analysis, Data curation. **Yuping Wang:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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