

The Impact of Bi-hemispheric iTBS Stimulation of the IPL and IFG on Social Reciprocity in ASD

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Abstract

ASD encompasses a wide range of limitations in reciprocal, social and communicative milestones. Given the significant limitations of the existing pharmacological interventions, use of non-invasive brain stimulation such as repetitive Transcranial Magnetic Stimulation (rTMS) has generated hope for mitigating ASD-related behaviors. Some experts attribute the limitations in social cognition in ASD to abnormal mirror neuron function or modulation. Mirror neurons are concentrated in the inferior frontal gyrus (IFG) and the inferior parietal lobule (IPL). Leveraging the hemispheric dependent function of mirror neurons, we aimed to investigate the impact of rTMS stimulation of the bilateral IFG and IPL on social reciprocity in ASD. We used the Childhood Autism Rating Scale, 2nd edition, high functioning (CARS2) as the outcome measure. The assessment was completed at baseline, in 3 weeks (phase I), 6 weeks (phase II) and 3 weeks after completion of TMS (phase III). A total of 6 ASD subjects (3 girls and 3 boys) with an average age of 14.8 years were recruited. Statistical analysis demonstrated a decrease in the total CARS2 scores commensurate with an improvement in social reciprocity/communication when comparing the baseline values to phase I (p<0.001), phase II (p<0.001), and phase III (p<0.001). This small experiment serves as a proof of principle for the novel approach of iTBS targeting the bilateral IPL/IFG as a therapeutic intervention in ASD.

Keywords: iTBS; Mirror neurons; IPL; IFG; Social reciprocity

Introduction

ASD encompasses a wide range of limitations in reciprocal, social and communicative milestones, as well as restrictive/repetitive behaviors, leading to significant life-time challenges [1,2].

ASD is a neurodevelopmental disorder with staggering clinical, social and financial burdens [3,4]. Attempts on understanding the underlying pathophysiology in ASD have led to two major schools

of thought: one focuses on the abnormalities of the mirror neurons and other cortical areas involved in reciprocity, while the other proposes a more widespread altered neuronal organization and dynamics. Those advocating for the former theory attribute the limitations in social cognition in ASD to abnormal mirror neuron function or modulation [5-11]. Mirror neurons are concentrated in the inferior frontal gyrus (IFG) and the inferior parietal lobule (IPL) [6]. Additional cortical regions involved in abstract social cognition include the medial prefrontal cortex (mPFC), temporal-parietal junction (TPJ) and posterior cingulate gyrus (pCG) [12-14] which all together comprise a "social reciprocity network" [15].

Given the significant limitations of the existing pharmacological interventions, use of non-invasive brain stimulation such as repetitive Transcranial Magnetic Stimulation (rTMS) [16] has generated hope for mitigating ASD-related behaviors. rTMS is a promising tool in neuropsychiatry [17,18] and has demonstrated safety in children [19,20]. The meta-analyses of the existing research suggest a modest improvement in some of the behavioral measures post rTMS in ASD [21,22]. While the protocols varied considerably, many used low frequency stimulation on the dorsolateral prefrontal cortex (DLPFC). This narrow focus of targeting DLPFC may preclude investigating other potential targets [23] such as the mirror neuron regions.

While the above rTMS based research studies have produced novel insights and yielded modest improvements in social relatedness and repetitive behaviors, we hypothesized that targeting the mirror neuron regions may provide additional insights and symptomatic improvement in ASD. There are very few studies using IPL or IFG as research/therapeutic targets [24-29]. Moreover, the existing body of literature attests to the hemispheric dependent function of the mirror neurons [30-32]. Leveraging this concept, we aimed to investigate the impact of rTMS stimulation of the bilateral IFG and IPL on social reciprocity in ASD.

This work followed our previous experiments of rTMS targeting the mirror neuron regions in ASD. Our feasibility study on 4 patients suggested that rTMS applied to the left-IPL may ameliorate social cognition. [33] More recently, we conducted a study applying 10 sessions of rTMS to the right or left IPL in subjects with ASD (DDD 604994, NCT 05371912) which demonstrated an improvement in social awareness [34].

Materials and Methods

This pilot project was funded by the Delaware Health Science Alliance (NCT 06807684) and conducted as a single-center, single-blind, sham controlled study to compare 2 parallel groups, active and sham at Christiana Care Health System in Delaware. The research protocol was approved by the Internal Review Board and the patients/parents signed the consent form to participate in this study.

A 3-week comparative study (phase I, control versus sham) was followed by an open-label 3-week period (phase II) where

subjects in the sham group were switched to active, and the active group continued to receive active treatment. The patients were randomized for participation in the two treatment arms. Each patient received a total of 18 sessions (3/week for 6 weeks) of active rTMS or sham on the bilateral IPL/IFG, using Magstim® Horizon®. We delivered intermittent theta burst stimulation (iTBS) 2400 stimulations/session equally divided between the right and left IPL and IFG. In our experience, the threshold for adequate cortical stimulation in this age group is between 48-52% of the maximum stimulator output. Therefore, for consistency and to assure applying a super-threshold stimulation, we utilized 55% of the maximum stimulator output for all patients [35].

For targeting the IPL and IFG we used the standard 10/20 electrode placement system via a commercial EEG cap. The IPL localizes to the P3/4 [36] and the IFG to F5/6 [23] electrodes. During the sham phase of the study, we implemented a standard shamming technique which consists of rotating the coil by 90 degrees [37]. The patients/families and the sub-investigator performing and interpreting the neuropsychological assessments remained blinded regarding the randomization for the 2 study arms.

Outcome measures

Childhood Autism Rating Scale, 2nd edition, high functioning (CARS2, HF): This is a 15-item scale, designed for ASD patients' level 1 and 2, 6-18 years old, implemented by a neuropsychologist to obtain quantitative behavioral measures based on patient's performance, as well as questionnaires soliciting parental input [38]. The testing was completed at the end of phase I and II and 3 weeks after completion of TMS (phase III).

SRS-2: The Social Responsiveness Scale – Second Edition (SRS-2) is a 65-item, caregiver-rated scale assessing social interaction and communication deficits [39]. The parents were asked to complete and submit the questionnaire electronically at the above intervals.

Data analysis

The CARS2 total scores across the study period were examined using a longitudinal Generalized Estimating Equation (GEE) model to account for within-subject correlation of repeated measures at four time points (Baseline, Phase I, Phase II, Phase III).

CARS2 total scores were modeled as a continuous outcome using a Gaussian distribution with an identity link. Fixed effects included treatment group, timepoint, and group by time interaction. The active/active group was the reference group. An exchangeable working correlation structure was specified as our data set was too small for stable AR(1) GEE.

To address small-sample bias in variance estimation, standard errors were obtained using a delete one cluster jackknife (Mancl & DeRouen 2001). All tests were two sided with statistical significance set at $p < 0.05$.

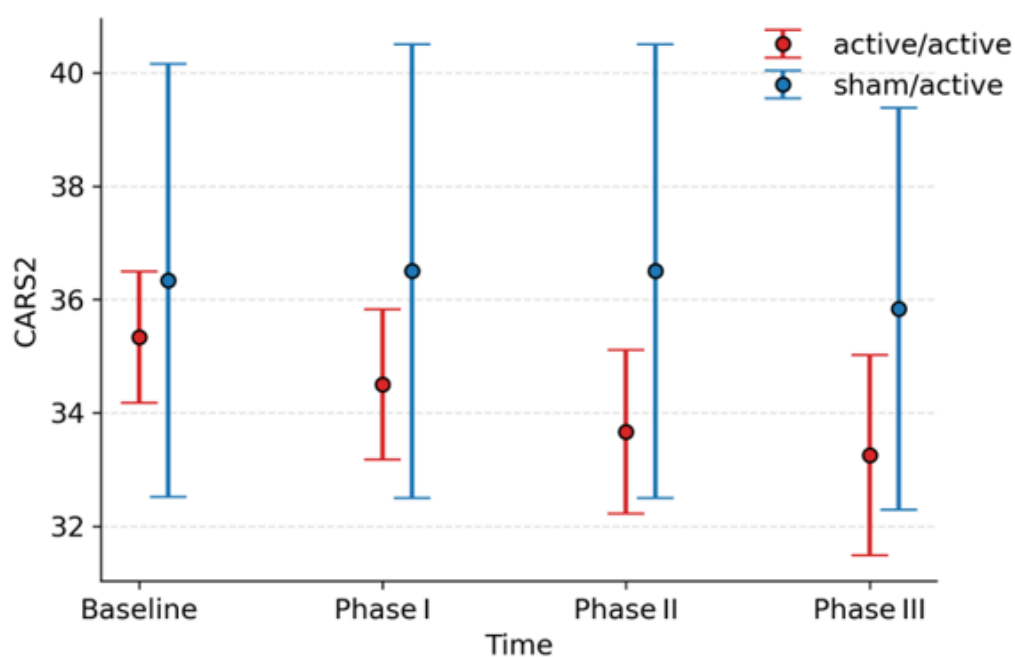
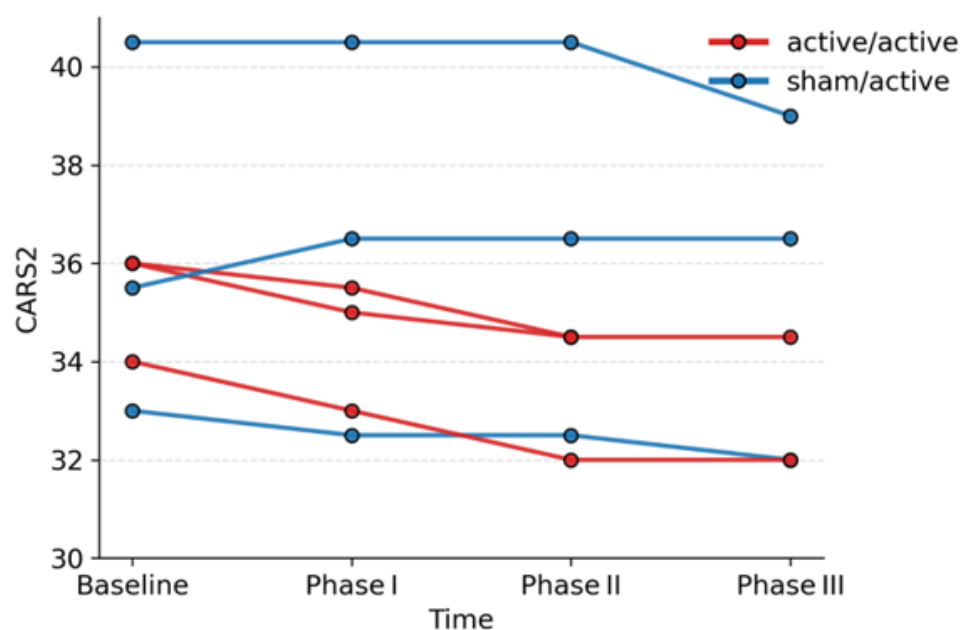


Figure 1: The trajectory of the CARS2 scores in the study subject. A negative β for the main effect of time indicates an improvement (decrease) in CARS2 score for the reference group (active/active). A positive β for the interaction indicates that the sham/active group showed less improvement compared to the active/active group.

Results

A total of 6 ASD subjects (3 girls and 3 boys) with an average age of 14.8 years were recruited between October 2024 to June

2025 and completed the study (table 2). None of the subjects experienced any adverse effects.

Table 1: Inclusion/exclusion criteria.

Inclusion criteria	
1.	Fulfilling the DSM-V criteria for ASD and confirmed by CARS2, HF
Exclusion criteria	
1.	Patients with ASD exhibiting significant anxiety or contact avoidance, precluding them from cooperating with the procedure
2.	Patients with a known diagnosis of seizures
3.	Presence of any metallic implants or devices in the head or neck area
4.	Pregnancy

Table 2: Study subjects.

Subjects Age/gender	Diagnosis	Randomization	Number of iTBS sessions
17/F	ASD II	active/active	18
14/M	ASD I	active/active	18
13/M	ASD I	sham/active	9
13/M	ASD II	sham/active	9
14/F	ASD I	active/active	18
18/F	ASD II	sham/active	9

The GEE analysis demonstrated a significant main effect of time, indicating an overall reduction in CARS2 scores. In the active/active group, the mean score decreased by 0.83 points at Phase I (JK-SE = 0.19, $p < 0.001$), 1.67 points at Phase II (JK-SE = 0.19, $p < 0.001$), and 1.69 points at Phase III (JK-SE = 0.32, $p < 0.001$) relative to the baseline. There was a significant group by time interaction. Positive interaction coefficients indicate less improvement in the sham/active group.

At Phase I, the between-group difference approached significance ($\beta = 1.00$, JK-SE = 0.53, $p = 0.058$). In Phase II, the

difference was significant; the sham/active group showed 1.83 points less reduction in scores ($\beta = 1.83$, JK-SE = 0.53, $p < 0.001$). In Phase III interaction was not significant ($\beta = 1.19$, JK-SE = 0.92, $p = 0.196$).

The parental reports using the SRS2 was uploaded by the parents at the end of each phase. Unfortunately, 50% of the data points were not completed and as such a statistical analysis was not possible. Moreover, given the small sample size, performing a statistical analysis on the different components of CARS2 was not possible.

Table 3: CARS2 mean and SD.

Study arm	Timepoint	Mean	SD
active/active	Baseline	35.33	1.15
	Phase I	34.5	1.32
	Phase II	33.67	1.44
	Phase III	33.25	1.77
sham/active	Baseline	36.33	3.81
	Phase I	36.5	4
	Phase II	36.5	4
	Phase III	35.83	3.55

Table 4: Jackknife GEE Results for CARS2.

Predictor	Coefficient (β)	JK-SE	95% CI	p-value
Intercept				
Baseline score (active/active group)	35.33	0.75	33.87 to 36.79	<0.001

Main Effects				
Group (sham/active vs. active/active) at Baseline	1	2.58	-4.05 to 6.05	0.698
Time (for active/active group vs. Baseline)				
Phase I	-0.83	0.19	-1.20 to -0.47	<0.001
Phase II	-1.67	0.19	-2.03 to -1.30	<0.001
Phase III	-1.69	0.32	-2.31 to -1.06	<0.001
Group × Time Interaction				
sham/active vs. active/active change from Baseline				
Phase I	1	0.53	-0.03 to 2.03	0.058
Phase II	1.83	0.53	0.80 to 2.87	<0.001
Phase III	1.19	0.92	-0.61 to 2.98	0.196

Discussion

We have recruited 6 subjects with ASD and administered iTBS stimulation of the bilateral IPL/IFG and demonstrated a decrease in the total CARS2 scores commensurate with an improvement in social reciprocity/communication. CARS2 is a semi quantitative assessment which evaluates social reciprocity, emotional responses as well as verbal and nonverbal communication. While we acknowledge the small sample size which limits the generalizability of our findings, we propose that conceptually speaking, targeting the bilateral “mirror neuron regions” such as IPL and IFG may be considered as a novel approach in designing rTMS treatment trials for ASD.

Despite the wealth of literature testifying to the role of mirror neurons in ASD and social cognition, [5-8] there are very few studies using IPL or IFG as research/therapeutic targets [24-29].

The hemispheric dependent function of mirror neurons is well recognized. While the left IFG is activated during observation of stimuli without an emotional component, the right IFG responds to the stimuli with an emotional component and hence contributes to experiencing empathy. Moreover, both the left IFG and IPL are involved in processing the verbal components of the social interactions and have a crucial role in the communication difficulties that characterize ASD. On the other hand, the right IPL is involved in multi-sensory integration/nonverbal communication. As such, while both the right and left IFG and IPL contribute to social cognition, they each orchestrate different elements of reciprocity [31,30,40]. We propose that leveraging the hemispheric dependent function of the IPL and IFG, such as bi-hemispheric stimulation of these areas, may allow for optimizing neurostimulation strategies.

Bi-hemispheric iTBS application in ASD is a novel approach and has been rarely attempted. Ni et al have spearheaded this line of work by conducting 2 separate studies implementing iTBS stimulation of the bilateral superior temporal sulcus in children and adults with ASD. While in their first experiment statistical significance was not reached, they demonstrated superiority of 8 weeks of intervention compared to 4 weeks [41]. In a more recent study of 13 adults with ASD they proposed potential therapeutic efficacy of this approach [42].

In our study, the subjects in the active/active arm had slightly lower CARS2 scores at baseline indicating a milder phenotype, which may have also contributed to the better outcome compared to the sham/active group. This finding is consistent with the previous observations reporting better treatment results produced by rTMS in individuals who are less severely affected [41]. The mechanisms of action of rTMS remain an area of significant investigation [43,44]. Our results have demonstrated longevity of the rTMS effects being sustained 3 weeks after the termination of the intervention, possibly attributable to an increased level of brain-derived neurotrophic factor leading to neuronal plasticity [45-47].

Conclusion

This small experiment serves as a proof of principle for the novel approach of iTBS targeting the bilateral IPL/IFG as a therapeutic intervention in ASD. Future studies with larger number of subjects are necessary to solidify this concept and further refine the approach. With continued investigation of the effects of rTMS and the neurobiological underpinnings of ASD, the future developments may eventually allow highly individualized neurostimulation approaches to treat ASD patients [48,49].

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Conflicts of Interest

None of the authors have any conflicts to disclose.

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