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Evaluating the feasibility, safety and efficacy of accelerated continuous theta-burst stimulation targeting the left primary motor cortex to improve social communication impairment in children with autism

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To the editor:

Social communication impairment (SCI) is a core symptom of autism spectrum disorder (ASD), and evidence-based interventions targeting this domain remain limited.[1] In the past decade, repetitive transcranial magnetic stimulation (rTMS), one of the most commonly applied non-invasive neurostimulation techniques, has shown efficacy in treating neuropsychiatric disorders, such as depression.[2] This success raised hope that rTMS could be a promising therapeutic intervention for ASD. Although prior trials have suggested the potential efficacy of rTMS in improving SCI in ASD, the results were inconclusive, largely due to considerable heterogeneity in stimulation protocols and methodological limitations.[3]

The primary motor cortex (M1) is crucial for action execution, emotion evaluation and language comprehension.[4 5] In addition, individuals with ASD exhibit atypical neuroplasticity profiles upon stimulation of M1.[6] These suggest that M1 could be a potential therapeutic target for addressing SCI in individuals with ASD. However, there has been no rTMS trial targeting M1 to examine its effects on ASD core symptoms. Most previous trials enrolled only autistic adults or children without intellectual disability, primarily due to the necessity of maintaining a prolonged stationary position during rTMS sessions.[3] Continuous theta-burst stimulation (cTBS), a novel form of rTMS, reduces the stimulation duration while achieving comparable or even superior neuromodulatory effects.[7] Moreover, the accelerated design, characterised by spaced sessions with higher pulse doses, may enhance and sustain neuromodulatory effects while reducing the treatment course to just a few days, potentially improving both compliance and overall efficacy.[8 9] We integrated these considerations and developed a novel accelerated cTBS (a-cTBS) protocol targeting the left M1 for therapeutic intervention and involvement of a broader autistic population. In this study, we conducted an open-label trial to assess the feasibility, safety and efficacy of the novel 5-day a-cTBS intervention among children with ASD (online supplemental figure S1).

Eligible participants were children aged 4–10 years with a clinical diagnosis of ASD (see details in online supplemental methods). The sample size calculation is presented in the supplemental material. Participating children were recruited from the outpatient clinic in the Department of Developmental and Behavioral & Child Primary Care of Xinhua Hospital, Shanghai, China. Clinical assessments were scheduled at three time points: pre-intervention, post-intervention and 1-month follow-up. The procedures and purposes of the study were explained face-to-face to all participants' legal guardians, who subsequently provided written informed consent. The trial was registered at ClinicalTrials.gov (NCT05472870).

A professionally trained physician was responsible for locating the target position and the resting motor threshold (RMT; detailed in online supplemental methods; online supplemental figure S2). During stimulation, the stimulus intensity was set to 80%

RMT. Triplet standard cTBS (1800 pulses, 120 s) were delivered hourly, and 10 sessions were performed per day (18 000 pulses/day) for 5 consecutive days (90 000 pulses in total; online supplemental figure S3).

The safety profiles were recorded by an open-ended interview for any adverse event or discomfort administered following each treatment session and follow-up. The primary efficacy outcome was the change in parent-reported Social Responsiveness Scale (SRS) over a 1-month period. SRS is widely used in measuring social impairment, with higher scores indicating more severe symptoms.[10] We also calculated five subscales of SRS as secondary outcomes. At the 1-month follow-up, a trained assessor administered a semistructured interview with the caregiver and used the Clinical Global Impression of Improvement (CGI-I) to rate the general improvement of symptoms relative to the baseline (a 7-point scale: 1='very much improved' to 7='very much worse').[11] Other secondary outcome measures include the Chinese Communicative Development Inventory (CCDI), the Peabody Picture Vocabulary Test (PPVT) and the Multilingual Assessment Instrument for Narratives (MAIN) at pre-intervention and 1-month follow-up. The CCDI is a caregiver-reported tool widely used to assess early vocabulary development and the language skills of older children with developmental disorders.[12] The PPVT is an assessor-rated standard test for measuring single-word comprehension.[13] The MAIN is a test to assess children's narrative abilities and comprehension through the telling/retelling of standard stories.[14]

To examine the potential efficacy of a-cTBS, we performed a post hoc analysis by comparing the longitudinal changes in SRS between the trial participants and a historical control group. The control group was identified from the Shanghai Autism Early Development (SAED) cohort who had completed both an initial SRS assessment at diagnosis and a voluntary follow-up SRS evaluation 30–50 days thereafter (aligned with the mean 40-day interval in the a-cTBS trial).[15] We excluded individuals exhibiting characteristics that were exclusive in only one group and then applied the inverse probability of treatment weighting (IPTW) approach to balance baseline characteristics, including sex, age, full-scale intelligence quotient and Childhood Autism Rating Scale (CARS), using the ipw package (V.1.2). We used the standardised mean difference (SMD) to assess the differences in baseline characteristics between the two groups before and after IPTW. Given the limited sample size, we applied an SMD threshold of less than 0.15 as an acceptable level of balance. We used a weighted longitudinal mixed-effect model to assess the average treatment effect of a-cTBS by the coefficient of the interaction term of a-cTBS (0 for control, 1 for treatment) × Time (0 for pretreatment, 1 for 1-month follow-up). Robust 95% confidence intervals (CIs) were estimated by bootstrap. The analyses were initially employed in the primary outcome, the SRS total score, and were then performed similarly in the five subscales of SRS. Additional analyses for the primary outcome included (1) a longitudinal mixed-effect model, in which time was coded as a continuous variable (in days), and (2) a weighted linear model adjusting for the baseline SRS total score.

After observing a potential treatment effect, we explored the characteristics of the changes in SRS during 1 month (ΔSRS_{1mon}) among all participants in the a-cTBS clinical trial (n=30 hereinafter). First, we qualitatively described the CGI-I scores and main features of the caregiver-reported changes in symptoms. Second, according to the median of the ΔSRS_{1mon}, we divided the participants into high- and low-response groups. We investigated whether changes in SRS appeared immediately after the 5-day intervention by applying a t-test comparing ΔSRS_{5day} to zero. In addition, we explored whether ΔSRS_{5day} was predictive of the response group and ΔSRS_{1mon} by logistic and linear regression, respectively. ΔSRS_{1mon} was considered as the outcome in the following analyses. Third, we tested the changes in children's language abilities (CCDI, PPVT and MAIN scores) from pretreatment to 1-month follow-up by comparing the differences to zero. Linear regression was employed to examine the associations of longitudinal changes in language abilities and ΔSRS_{1mon}. Lastly, we applied the linear regression to investigate whether the baseline characteristics were predictive of ΔSRS_{1mon}. All statistical analyses were conducted using SPSS V. 25.0 and R V.4.3.2.

From July 2022 to December 2022, we assessed 36 children with ASD for eligibility and enrolled 30 children. All participants completed the full intervention course and follow-up assessments for the primary outcome measure (see online supplemental figure S1; Online supplemental table S1). Adverse events were reported in 10 (33%) of the 30 trial participants, including agitation (six cases), scalp pain (three cases) and nausea (one case). All adverse events were rated as mild and resolved spontaneously.

IPTW yielded comparable clinical characteristics between the trial participants and the historical control group (online supplemental table S2). The mean score of SRS in the a-cTBS group declined from an average of 95.76 (standard deviation (SD) 20.06) at baseline to 78.52 (SD 19.71; p<0.001) at the 1-month follow-up. Meanwhile, the historical control group showed generally stable SRS scores (mean (SD) at baseline, 94.75 (20.29); mean (SD) at the 1-month follow-up, 95.04 (19.37); p=0.879; figure 1A). After IPTW, a-cTBS was associated with a reduction of 17.44 points (p<0.001) in the SRS total score at the 1-month follow-up (online supplemental table S3). Similar declines were observed in the five subscales of SRS (online supplemental table S3 and figure S4). Alternative modelling strategies yielded consistent results (online supplemental table S4).

Caregivers of the children who underwent a-cTBS mostly reported an overall improvement in

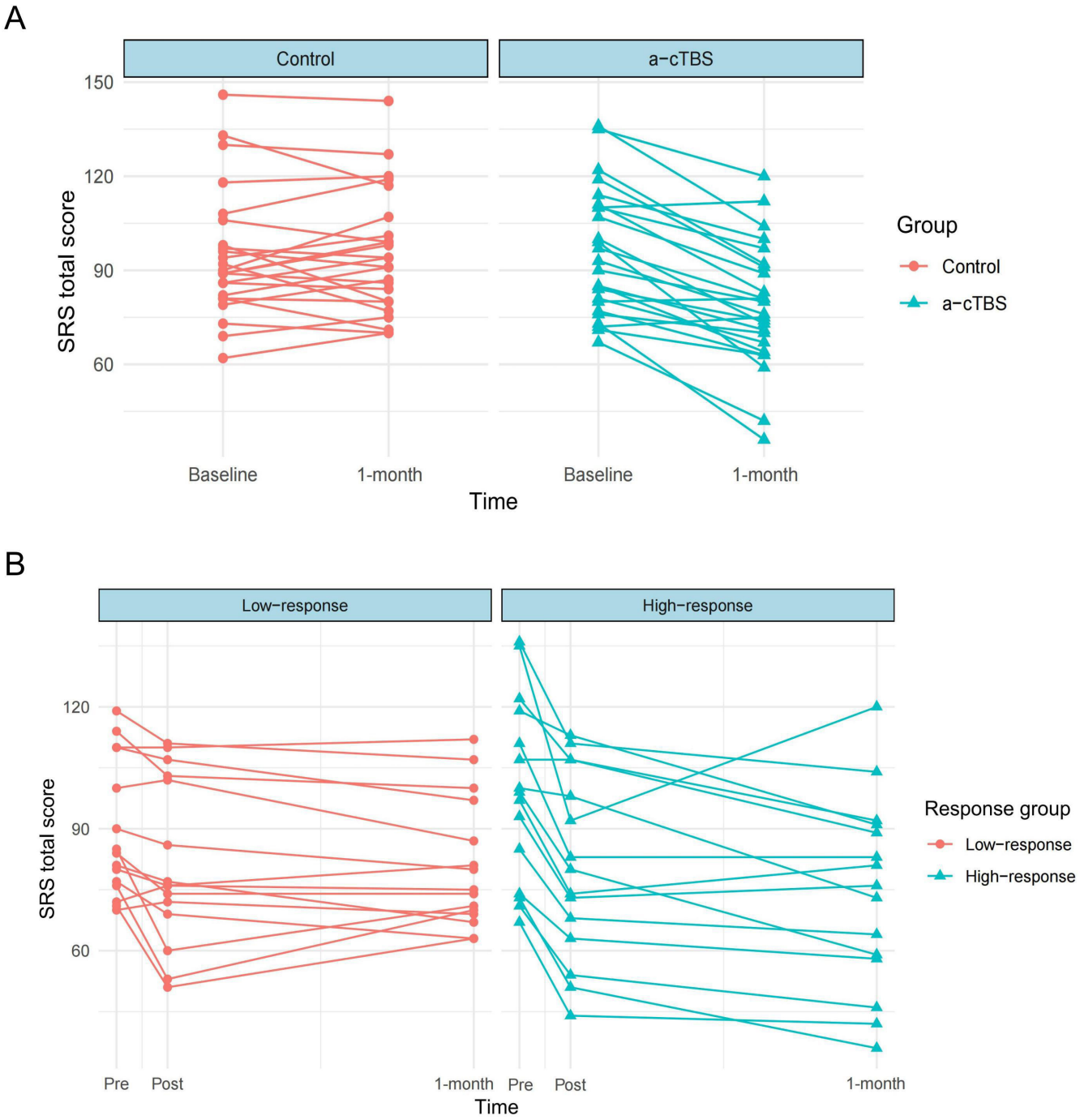

Figure 1 (A) Changes in the SRS total score from baseline to the 1-month follow-up between the a-cTBS and historical control groups. (B) Longitudinal patterns of SRS total scores measured at pre-treatment, post-treatment and 1-month follow-up, among participants of the a-cTBS trial, dichotomised by the median of ΔSRS_{1mon}. a-cTBS, accelerated continuous theta-burst stimulation; SRS, Social Responsiveness Scale; ΔSRS_{1mon}, SRS_{1mon} - SRS_{base}.

symptoms of their children at the 1-month follow-up as measured by CGI-I; 5 of 30 (17%) participants were rated as 'improved' and 22 (73%) 'slightly improved' (online supplemental table S5). The qualitative interview showed that multiple caregivers mentioned improvements in the social and/or language domains (online supplemental table S5). By dichotomising the participants into high- and low-response groups based on the median of SRS changes during 1 month (ΔSRS_{1mon}, median −14.50), we found that children in the high-response group generally showed a reduction in SRS immediately after the 5-day treatment (figure 1B; mean ΔSRS_{5day} −18.07, SD 10.79, p<0.001; mean ΔSRS_{1mon} −25.00, SD 7.82, p<0.001), while children in the low-response group showed a lower level of reduction after treatment (ΔSRS_{5day}, mean −7.47, SD 9.05, p=0.006; ΔSRS_{1mon}, mean −8.20, SD 6.39, p<0.001). ΔSRS_{5day} was highly correlated with ΔSRS_{1mon} (r=0.44, p=0.014). A more prominent ΔSRS_{5day} was predictive of high response at the 1-month follow-up

Table 1 The longitudinal changes in language abilities and their correlation with ΔSRS_{1mon} among children with ASD aged 4–10 years receiving the a-cTBS intervention

		Longitudinal change				Correlation between longitudinal change and ΔSRS_{1mon}	
Outcome	n	Baseline, mean (SD)/median (IQR)	1-month follow-up, mean (SD)/median (IQR)	Statistic value	P value*	Adjusted β† (95% CI)	P value
PPVT	27						
PPVT raw score		67.78 (27.23)	76.11 (26.89)	−3.80	**<0.001**	−0.30 (−0.68 to 0.08)	0.114
PPVT IQ		100.63 (28.74)	111.00 (30.89)	−3.62	**0.001**	−0.23 (−0.52 to 0.06)	0.110
CCDI	22						
Words produced		733.00 (615.25, 789.50)	771.50 (657.00, 793.25)	−3.25	**0.001**	−0.02 (−0.18 to 0.14)	0.789
Sentence complexity		69.00 (42.00, 76.00)	71.00 (54.00, 79.00)	−1.81	0.070	−0.10 (−0.54 to 0.33)	0.631
MAIN_Telling	14						
Story structure		7.57 (2.34)	8.96 (2.43)	−2.71	**0.018**	1.12 (−2.24 to 4.48)	0.479
Structural complexity		2.11 (0.59)	2.50 (0.55)	−1.92	0.054	0.87 (−9.15 to 10.89)	0.852
Internal states terms		3.68 (2.00)	5.21 (3.20)	−2.37	**0.018**	1.17 (−1.68 to 4.03)	0.385
Comprehension questions		6.50 (1.79)	8.32 (1.56)	−5.39	**<0.001**	−1.40 (−6.93 to 4.13)	0.589
MAIN_Retelling	14						
Story structure		9.07 (2.18)	12.21 (2.28)	−5.40	**<0.001**	1.16 (−1.77 to 4.09)	0.403
Structural complexity		2.32 (0.58)	2.75 (0.38)	−2.07	**0.039**	4.73 (−3.86 to 13.32)	0.251
Internal states terms		5.07 (2.13)	6.14 (1.56)	−1.93	0.054	0.92 (−2.38 to 4.23)	0.552
Comprehension questions		6.46 (1.96)	8.21 (1.66)	−3.87	**0.002**	−2.38 (−5.92 to 1.16)	0.167

*A Wilcoxon test was used for the CCDI outcomes, and a paired-sample t-test was used for the PPVT outcomes. A Wilcoxon test or a paired-sample t-test was used for the MAIN outcomes.
†Adjusted for the baseline SRS total score.
a-cTBS, accelerated continuous theta-burst stimulation; ASD, autism spectrum disorder; CCDI, Chinese Communicative Development Inventory; CI, confidence interval; IQ, intelligence quotient; IQR, interquartile range; MAIN, Multilingual Assessment Instrument for Narratives; PPVT, Peabody Picture Vocabulary Test; SD, standard deviation; SRS, Social Responsiveness Scale; ΔSRS_{1mon}, SRS_{1mon} - SRS_{base}.

(OR 0.89; 95% CI 0.81 to 0.97, p=0.016). The association was consistently observed when additionally adjusted for pretreatment SRS (OR 0.88; 95% CI 0.78 to 0.97, p=0.016).

We further examined the changes in language ability at the 1-month follow-up (table 1). The raw scores for PPVT improved from a mean (SD) of 67.78 (27.23) at baseline to 76.11 (26.89) (p<0.001) at the 1-month follow-up. The PPVT IQ improved from a mean (SD) of 100.63 (28.74) to 111.00 (30.89) (p=0.001). In addition, the words produced score of CCDI improved from a median (interquartile range (IQR)) of 733.00 (615.25 to 789.50) at baseline to 771.50 (657.00 to 793.25) (p=0.001) at the 1-month follow-up, while the change in the CCDI sentence complexity score only showed a trend of improvement (p=0.07). We then assessed the correlation between the longitudinal change in language ability and ΔSRS_{1mon}. A more prominent improvement in PPVT showed a trend with a greater response in ΔSRS_{1mon}, although the 95% CI crossed zero (table 1). The MAIN test was assessed only in 14 children with sufficient expressive ability. The limited sample size prevented further interpretation of meaningful trends. We did not find potential predictors of ΔSRS_{1mon} among candidate variables at baseline, including age, sex, CARS, verbal IQ, performance IQ, full-scale IQ and language ability measurements (online supplemental table S6).

In summary, our findings showed that 5-day a-cTBS targeting the left M1 in children with ASD is feasible, safe and might have a treatment effect on SCI. Specifically, this effect was observed immediately after the 5-day treatment and persisted up to the 1-month follow-up. Additionally, greater responsiveness in the 1-month changes in SRS showed a trend toward an increase in single-word comprehension scores.

Our study has several strengths. First, the novel neurostimulation protocol addressed the research gap

by including young children and children with intellectual disabilities, populations that are often underrepresented in similar studies. Second, we observed a potential treatment effect of a-cTBS targeting the left M1 on SCI in children with ASD, suggesting M1 may be a candidate therapeutic target for ASD. Moreover, in our protocol, M1 is easy to localise by motor-evoked potential measurement instead of neurological navigation, which confers practical advantages in a clinical setting. Third, compared with behavioural interventions for children with ASD, such as applied behaviour analysis that requires intensive engagement with professional therapists for several years, our neurostimulation protocol is easier to operate and more generalisable. Limitations of this study include its open-label design, the potential influence of the placebo effect and the absence of supplemental objective measurement tools for assessing social impairment. Future randomised controlled trials are warranted to more rigorously evaluate the therapeutic efficacy.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki and approved by the Xinhua Hospital Ethics Committee (XHEC-C-2022-008-4). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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