Accelerated continuous theta burst stimulation targeting left primary motor cortex for children with autism spectrum disorder: multicentre randomised sham controlled trial

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ABSTRACT

OBJECTIVES

To investigate the efficacy and safety of a five day accelerated continuous theta burst stimulation (a-cTBS) protocol in improving social communication impairment in children with autism spectrum disorder.

DESIGN

Multicentre randomised sham controlled trial.

SETTING

Three academic hospitals across three provinces in China, conducted from July 2023 to October 2024.

PARTICIPANTS

200 children aged 4-10 years with autism spectrum disorder (167 boys and 33 girls) all with a full scale intelligence quotient ≥50.

INTERVENTIONS

Participants were randomised 1:1 to receive active a-cTBS (n=100) or sham (n=100) treatment stratified by full scale intelligence quotient (≥70 or <70) and study site. Participants received 10 sessions each day for five consecutive days, targeting the left primary motor cortex. Participants and evaluators were masked to interventions.

MAIN OUTCOME MEASURES

Two primary outcomes were assessed using the Social Responsiveness Scale, second edition (SRS-2): changes in social communication impairment from baseline to post-intervention and from baseline to one month follow-up. Primary analyses were conducted on a modified intention-to-treat population, including participants who received at least one stimulation session. Secondary outcomes included language improvements assessed from baseline to one month follow-up and changes in SRS-2 subscales.

RESULTS

Of the 200 participants, 198 were included in the modified intention-to-treat analysis (99 in each group) and 193 completed the full intervention. Compared with the sham group, the a-cTBS group showed significantly greater reductions in SRS-2 scores post-intervention (−6.25, 95% confidence interval −8.69 to −3.81; Cohen's d −0.92; P<0.001) and at one month follow-up (−6.17, −8.65 to −3.70; −0.90; P<0.001). Secondary outcomes also favoured a-cTBS, with significant improvements observed in language abilities (Cohen's d 0.12-0.47; all P<0.02; measured by Multilingual Assessment Instrument for Narratives). Reported adverse events were all mild to moderate and resolved without intervention.

CONCLUSIONS

A five day a-cTBS protocol targeting the left primary motor cortex significantly improved social communication in children with autism spectrum disorder and showed a favourable safety profile. These findings support a-cTBS as a viable and scalable therapeutic option for children with autism spectrum disorder.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05927792

WHAT IS ALREADY KNOWN ON THIS TOPIC

Social communication impairment, a core symptom of autism spectrum disorder, lacks effective treatments

Non-invasive neurostimulation techniques have shown potential in modulating neural network plasticity and improving symptoms of autism spectrum disorder, but existing evidence remains limited and inconclusive

Preliminary results from a previous open label pilot study suggested that a new accelerated continuous theta burst stimulation (a-cTBS) protocol targeting the left primary motor cortex is feasible, safe, and potentially effective in enhancing social communication in children with autism spectrum disorder

WHAT THIS STUDY ADDS

This randomised, sham controlled trial showed that a five day a-cTBS protocol targeting the left primary motor cortex significantly improves social communication in children with autism spectrum disorder

The protocol's operational simplicity, combined with consistent treatment effects across diverse subgroups, underscores its potential for broader clinical implementation

Adverse effects were mild to moderate and all resolved spontaneously without the need for intervention, supporting the safety and tolerability of the intervention

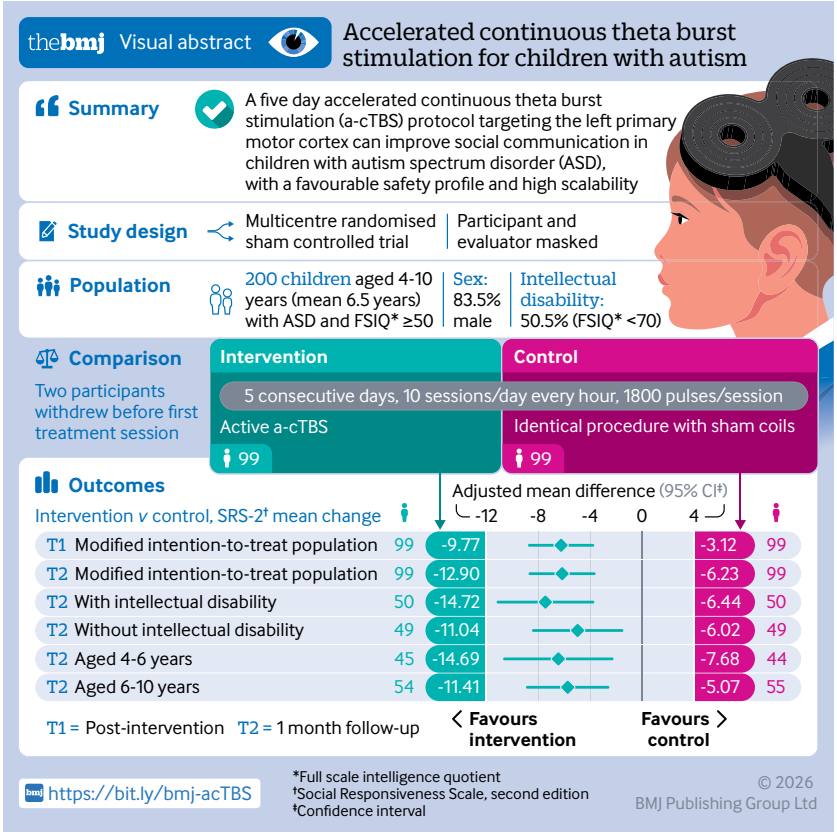
Introduction

Autism spectrum disorder (ASD) represents a major global health challenge, ranking among the top 10 causes of non-fatal health burden in children and adolescents younger than 20 years,[1] with incidence continuing to rise worldwide.[2] Social communication impairment, a core manifestation of ASD, profoundly affects the daily functioning and psychological wellbeing of people with ASD.[3] While behavioural interventions remain the only evidence based treatment for improving social communication impairment, their effectiveness varies considerably.[4 5] The optimal

outcomes are typically observed in people with ASD and without co-occurring intellectual disability who receive early, intensive intervention.[5] However, intellectual disability affects 33% of people with ASD,[6] effectively leaving one third of the population with ASD without viable treatment options. Furthermore, early and intensive behavioural interventions require substantial financial resources,[3] limiting their accessibility, particularly in low resource settings. These challenges underscore a substantial therapeutic gap and highlight the urgent need for safe, effective, and scalable interventions that can serve a broader range of the population with ASD.

Over the past decade, repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurostimulation technique, has shown clinical efficacy and a favourable safety profile in treating various neuropsychiatric conditions, including depression.[7 8] The ability of this technique to modulate neuroplasticity and functional connectivity has led to growing interest in its application to ASD.[8 9] However, current empirical evidence remains limited and inconclusive.[10-15] Because conventional rTMS protocols require sustained stationary positioning during neuronavigation and stimulation procedures, participant recruitment has been largely confined to adolescents and adults with ASD and without comorbid intellectual disability who can maintain adequate compliance. The systematic exclusion of people with comorbid intellectual disability undermines the ecological validity and generalisability of findings, given the high comorbidity rate.[3 16] Additionally, the systematic exclusion of young children may result in missing a critical intervention window for optimal efficacy because early childhood represents a period marked by heightened neuroplasticity and therapeutic potential.[17 18]

To address these challenges, we developed and evaluated a rTMS protocol adapted for young children with ASD and children with co-occurring intellectual disability. In an open label pilot trial, this protocol showed feasibility, safety, and promising improvements in social communication among children with ASD.[19] We selected the left primary motor cortex (M1) as the stimulation target based on mechanistic and practical considerations. Accumulating evidence highlighted the roles of M1 in regulating action understanding, language processing, and social emotional functions—domains frequently affected in autism.[20-22] Motor cortex excitation or inhibition imbalances and altered motor networks are recognised as common neural abnormalities in ASD, and the motor evoked potential activity from M1 may serve as a predictive biomarker of ASD.[23-25] Our earlier pilot study showed that targeting M1 specifically improved social deficits in children with ASD.[19] In clinical practice of rTMS treatment, M1 can be accurately targeted using motor evoked potential detection, which largely eliminates the need for complex neuronavigation systems and improves its feasibility in the paediatric population, including those with intellectual disability. To further optimise treatment adherence, we adopted an accelerated continuous theta burst stimulation (a-cTBS) protocol of rTMS. This design delivers a high cumulative dose of stimulation within a condensed time frame. The protocol reduces individual stimulation sessions from conventional durations to mere minutes, while condensing the overall treatment course from weeks or months to five days, without compromising therapeutic efficacy.[26-29] Building upon our previous study, we conducted this multicentre randomised controlled trial to evaluate the efficacy of the five day a-cTBS protocol in improving social communication among children with ASD, including those of younger age and those with intellectual disability.



Methods

Trial design

This investigator initiated, participant and evaluator masked, sham controlled, multicentre randomised clinical trial was conducted at three tertiary hospitals in Shanghai, Shandong, and Henan between July 2023 and October 2024. The trial protocol was approved by the ethics committees of all participating sites, including Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Qilu Hospital affiliated to Shandong University, and Zhengzhou Children's Hospital affiliated to Zhengzhou University. Written informed consent was obtained from the legal guardians of all participants after a thorough in-person explanation of the study procedures. The supplementary appendix gives additional methodological details

and the history of protocol modifications. This study followed the CONSORT (consolidated standards of reporting trials) guidelines and was preregistered on ClinicalTrials.gov (NCT05927792).

Study population

Participants were recruited at each participating site using two approaches: recruitment advertisements posted in the outpatient clinics of the Department of Developmental and Behavioural and Child Primary Care, and systematic screening of local clinical registries of children diagnosed with ASD. Further details are provided in the study protocol in the supplementary appendix.

Eligible participants were children with ASD aged 4-10 years with a full scale intelligence quotient of 50 or higher. ASD diagnoses were based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition,[30] and were confirmed using the Autism Diagnostic Observation Schedule or the Autism Diagnostic Interview-revised.[31] Full scale intelligence quotient was assessed using standardised age appropriate versions of the Wechsler Intelligence Scale—the Wechsler Intelligence Scale for Children-revised for participants aged ≥6 years or the Wechsler Preschool and Primary Scale of Intelligence for those aged 4-6 years.[32 33] A full scale intelligence quotient <70 indicates comorbid intellectual disability and represents the conventional cutoff used to define high functioning and low functioning ASD.[34 35] A quotient ≥50 was required to ensure adequate cooperation with study procedures and to minimise ASD diagnostic uncertainty related to moderate to severe intellectual disability, consistent with previous studies.[36 37]

Exclusion criteria included a history of neurological diseases (eg, epilepsy), a diagnosis of psychiatric disorders other than ASD (eg, very early onset schizophrenia), genetic or chromosomal abnormalities, severe heart disease or hearing impairment, structural brain abnormalities requiring surgical treatment, metal implants in the head or neck, starting new interventions or treatments within four weeks before enrolment, or participation in other clinical trials. Participants with co-occurring attention deficit hyperactivity disorder were not excluded, given the high comorbidity and potential shared causes with ASD. All participants maintained stable regimens of psychotropic drugs throughout the study, with no dose modification permitted.

Interventions

All sites used the same model of pulsed magnetic stimulation device (M-100 Ultimate, Shenzhen Yingchi Technology Co., China). Operators administering stimulation underwent standardised training at Xinhua Hospital to ensure protocol consistency. The stimulation target was the left M1, identified as the motor hot spot that consistently evoked the largest motor evoked potential in the right abductor pollicis brevis muscle. The resting motor threshold was defined as the lowest transcranial magnetic stimulation intensity that elicited a motor evoked potential >50 μV in at least five out of 10 stimuli recorded from the corresponding muscle at rest.[38] This targeting procedure was identically applied in the active and sham groups.

During each stimulation session, the child was seated in a chair and instructed to keep the head still. The stimulation coil was positioned tangentially over the left M1 with the handle angled 45° posterior to the mid-sagittal plane. The stimulus intensity was set to 80% of resting motor threshold. The a-cTBS protocol consisted of 60 cycles of 10 bursts (each burst containing three pulses at 50 Hz), repeated every 200 ms, following the standard triplet cTBS pattern (detailed in supplementary methods). This protocol delivered a total of 1800 pulses over 120 s per session. Stimulation sessions were performed hourly, with 10 sessions per day (18 000 pulses per day) over five consecutive days, for a total of 90 000 pulses.[29]

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive active a-cTBS or sham stimulation. Randomisation was stratified by full scale intelligence quotient level (≥70 or <70) and trial site, using a block randomisation sequence (block length=4) generated by an independent coordinator in SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Treatment allocation was concealed from participants and evaluators through a masked implementation process. Only the intervention operators directly administering the intervention were unmasked to group assignments for the purpose of administering stimulation. Designated research coordinators, independent of assessments and interventions, oversaw this allocation process and ensured masking integrity (details in the study protocol in the supplementary appendix). All other on-site study personnel, including site investigators, study coordinators, and evaluators, as well as participants and their guardians, were masked to group assignment throughout the study.

To maintain the masking of participants and study personnel, sham coils were used that were visually indistinguishable from the active coils. These coils were modified by the manufacturer with shielding layers that blocked the magnetic field while preserving auditory and tactile cues, such as noise and vibration. Masking integrity was assessed at the one month follow-up by asking caregivers to identify the treatment arm they believed their child had been assigned to (active or sham).

Primary and secondary outcomes

Clinical outcome measures were evaluated at three time points. Baseline (T0) measurements were taken before the start of the intervention. Post-intervention measurements (T1) were collected within three days after completing the five day intervention. The one month follow-up assessment (T2) was conducted 30±7 days after completing the intervention. The schedule was consistent with previous rTMS studies in ASD.[11 14]

To ensure consistency in reporting, the same caregiver was required to complete all parent reported measures.

The primary outcome was defined as the change in the total score of the Social Responsiveness Scale, second edition (SRS-2, school age version) from T0 to T1 and from T0 to T2.[39] Our pilot trial showed a potential impact of a-cTBS on improving social communication, but showed no effect on restrictive, repetitive behaviour, the other core symptom of ASD.[19] The SRS-2 is a widely used caregiver reported instrument that quantifies the severity of social deficits of ASD. The scale comprises 65 items rated on a four point Likert scale (from 0=not true to 3=almost always true), yielding a total score (0-195) that reflects the overall level of autistic traits, with higher scores indicating greater impairment. The measure has been validated across clinical and community samples and is sensitive to treatment related change in ASD intervention trials.[40-43]

Prespecified secondary outcomes included changes from T0 to T2 in the composite score and domain standard scores (communication, daily living skills, and socialisation) of the Vineland Adaptive Behaviour Scale, third edition (Vineland-3, parent/caregiver form).[44] The Clinical Global Impression of Improvement (CGI-I) scale was applied to assess overall autistic symptom change of the child at T1 and T2 compared with the pre-intervention status.[45] Language improvements were assessed from T0 to T2 using three measures: the Multilingual Assessment Instrument for Narratives (MAIN),[46] the Chinese Communicative Development Inventory (CCDI),[47] and the Peabody Picture Vocabulary Test (PPVT).[48] Secondary outcomes also included changes in the five SRS-2 subscales: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviours. The supplementary methods give detailed descriptions of these instruments.

Safety and tolerability measures

To improve tolerability, during screening, children participated in a familiarisation session involving mock stimulation, and only those showing adequate tolerance were enrolled (details in supplementary methods). Adverse events were monitored using a structured, multistepped approach tailored to the developmental and communication profiles of children with ASD, given the challenges of assessing subjective experiences in children with communication difficulties. This protocol integrated three complementary sources of information to maximise the detection of objective and subjective adverse events, including child self-report, systematic behavioural observation, and in-depth caregiver interviews.

For all participants who received stimulation, semi-structured safety interviews were conducted immediately after each treatment session and at follow-up visits. The interview process began with an open ended question to elicit any discomfort or unusual experiences, followed by closed ended prompts addressing common transcranial magnetic stimulation related sensations (eg, scalp discomfort, dizziness, auditory discomfort). To accommodate communication difficulties, interviews with children used simple and concrete language. Clinicians also applied behavioural observations (eg, avoidance of returning for stimulation) as potential non-verbal indicators of discomfort. In parallel, caregivers were systematically interviewed about any symptoms or behavioural changes they observed during the intervention and follow-up period, providing continuous monitoring in the home environment. The supplementary appendix provides the full, detailed procedure.

All reported events, whether identified through child report, caregiver report, or behavioural observation, were documented in detail and graded by severity (mild, moderate, severe) according to predefined criteria. Each site had a neurologist available to evaluate any severe or concerning events and determine whether further assessment or intervention was required.

Statistical analysis

Sample size estimation was based on our previous single arm a-cTBS trial,[19] which showed a mean change in SRS-2 score of 8.5 (standard deviation 17.7). Using a two sided α=0.025 to account for two primary outcomes, and assuming 80% power and 10% attrition, the required sample size was 186 participants.[49] We decided to enrol 200 participants, with a priori proportional allocation across sites based on patient volume (proportional allocation 9:7:4 across Shanghai, Shandong, and Henan, respectively).

Primary analyses were conducted on the modified intention-to-treat population, defined as participants who received at least one stimulation session. In response to peer review, several post hoc modifications were made to improve the original statistical analysis plan, including the use of multiple imputation and additional covariate adjustments. These modifications were summarised at the end of the statistical analysis plan appendix and did not alter the conclusions of the prespecified analyses. SRS-2 change scores (T0 to T1 and T0 to T2) were considered continuous,[39 42 43] and the group differences in changes were assessed using linear regression, adjusting for baseline SRS-2 scores. All analyses included additional adjustments for the stratification factors (study site and intellectual disability status) unless explicitly stated otherwise. For missing follow-up data, multiple imputation was applied (imputation number 10; detailed in the supplementary methods).[50] Sensitivity analyses comprised a per protocol analysis including only participants who completed all five days of the intervention; a mixed effects model with random intercept for each participant (details in supplementary methods); and a complete case analysis.

Although the minimal clinically important difference (MCID) is crucial for interpreting intervention outcomes, no MCID has been established for the

SRS-2 in ASD populations. We estimated an MCID using an anchor based approach based on data from three previous clinical trials in children with ASD (n=121).[19 51 52] Using the CGI-I scale as the anchor, we defined the MCID as the mean difference in SRS-2 change scores between patients rated as "minimally improved" and those rated as "no change."[53] This analysis yielded an estimated MCID of 5.61 points. Detailed methods are provided in the supplementary methods. Treatment effects exceeding this value may be considered to be clinically meaningful. To account for potential baseline differences between groups, we conducted inverse probability weighting analyses, incorporating age, sex, comorbid with intellectual disability, study site, and baseline SRS-2 scores.[54] Balance between groups was assessed using standardised mean differences, with values less than 0.10 indicating adequate balance. To address the potential expectancy effect, we conducted a sensitivity analysis comparing nested regression models of SRS-2 change scores.[55] The base model included only parental guesses, while the expanded model incorporated parental guesses and actual treatment allocation. A significant improvement in model fit with the addition of true treatment assignment would indicate true treatment effects beyond the expectancy effect. Model fit comparisons were conducted using analysis of variance.

For continuous secondary outcomes (Vineland-3, PPVT, CCDI, and MAIN), linear regression was applied to estimate the mean differences between the intervention and control groups, adjusting for baseline scores. Ordinal outcomes (CGI-I ratings) were compared using ordinal logistic regression. Associations between primary and secondary outcomes were examined using linear regression. Secondary outcomes were considered exploratory and no adjustments for multiplicity were applied. Prespecified exploratory subgroup analyses were stratified by study site, intellectual disability status (full scale intelligence quotient ≥70 and <70), sex, age (4-6 and ≥6 years), and ASD severity (based on the median of Autism Diagnostic Observation Schedule social affect scores). Subgroup analyses were conducted by fitting linear models that included an interaction term between each subgroup factor and treatment allocation. The models assessed differential treatment effects across subgroups through P for interaction. Stratified analyses were performed within each subgroup. All statistical analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

The research specifically targeted social communication impairment, which is a core symptom of ASD and has been consistently identified as a priority research area by the autism community.[56 57] We engaged the parents of children with autism who attended our clinics to confirm that social communication impairment was also a concern of their child and family. In future studies, we hope to conduct more formal patient and public involvement with, for example, study design because we recognise it is an important component. We hope that more formal patient and public involvement procedures will become more common in China in the future.

Results

Baseline characteristics

Between July 2023 and September 2024, 286 children were screened, and 200 eligible participants (mean age 6.5±1.6 years; 83.5% male), all of whom were diagnosed with ASD using the Autism Diagnostic Observation Schedule, were randomised to receive active a-cTBS or sham treatment (n=100 per group; fig 1, table 1). None of the participants had a history of transcranial magnetic stimulation intervention. 50.5% of participants had co-occurring intellectual disability (full scale intelligence quotient <70), a population often excluded from neuromodulation trials.[10] Two participants withdrew before the first treatment session, resulting in a modified intention-to-treat population of 198 participants (99 *v* 99). A total of 193 participants (96.5%) completed the full five day intervention course. All participants in the modified intention-to-treat population were successfully contacted and had at least completed evaluator interviews and safety assessments at follow-ups. The primary outcome was completed by 194 participants (97.0%) at post-intervention (T1) and 197 participants (98.5%) at one month follow-up (T2).

Primary efficacy outcome

In the modified intention-to-treat population, SRS-2 total scores decreased by an average of 9.77 points (standard deviation 10.44) at T1 and 12.90 points (10.26) at T2 in the active a-cTBS group compared with reductions of 3.12 points (6.66) and 6.23 points (7.25), respectively, in the sham group. We observed a significant treatment effect of a-cTBS on social communication impairment, with a mean difference in SRS-2 scores of −6.25 (95% confidence interval (CI) −8.69 to −3.81; Cohen's d −0.92; P<0.001) at T1 and −6.17 (−8.65 to −3.70; −0.90; P<0.001) at T2 (fig 2). The average treatment effects were higher than the estimated MCID on SRS-2 (−5.61 points, supplementary methods). These results remained consistent across sensitivity analyses in the per protocol population (n=193; supplementary table S1), using mixed effects models (supplementary table S2), and in the complete case analysis (supplementary table S3).

Baseline SRS-2 total scores were 84.28 (standard deviation 21.40) in the a-cTBS group and 78.85 (20.40) in the sham group. In the additional analysis accounting for potential baseline difference, inverse probability weighting successfully achieved balance across baseline characteristics (all standardised mean differences <0.10), including baseline SRS-2 scores (active 82.1±20.8; sham 82.4 ±21.8; supplementary table S4). The weighted analysis showed treatment effects consistent with our primary findings (supplementary table S5).

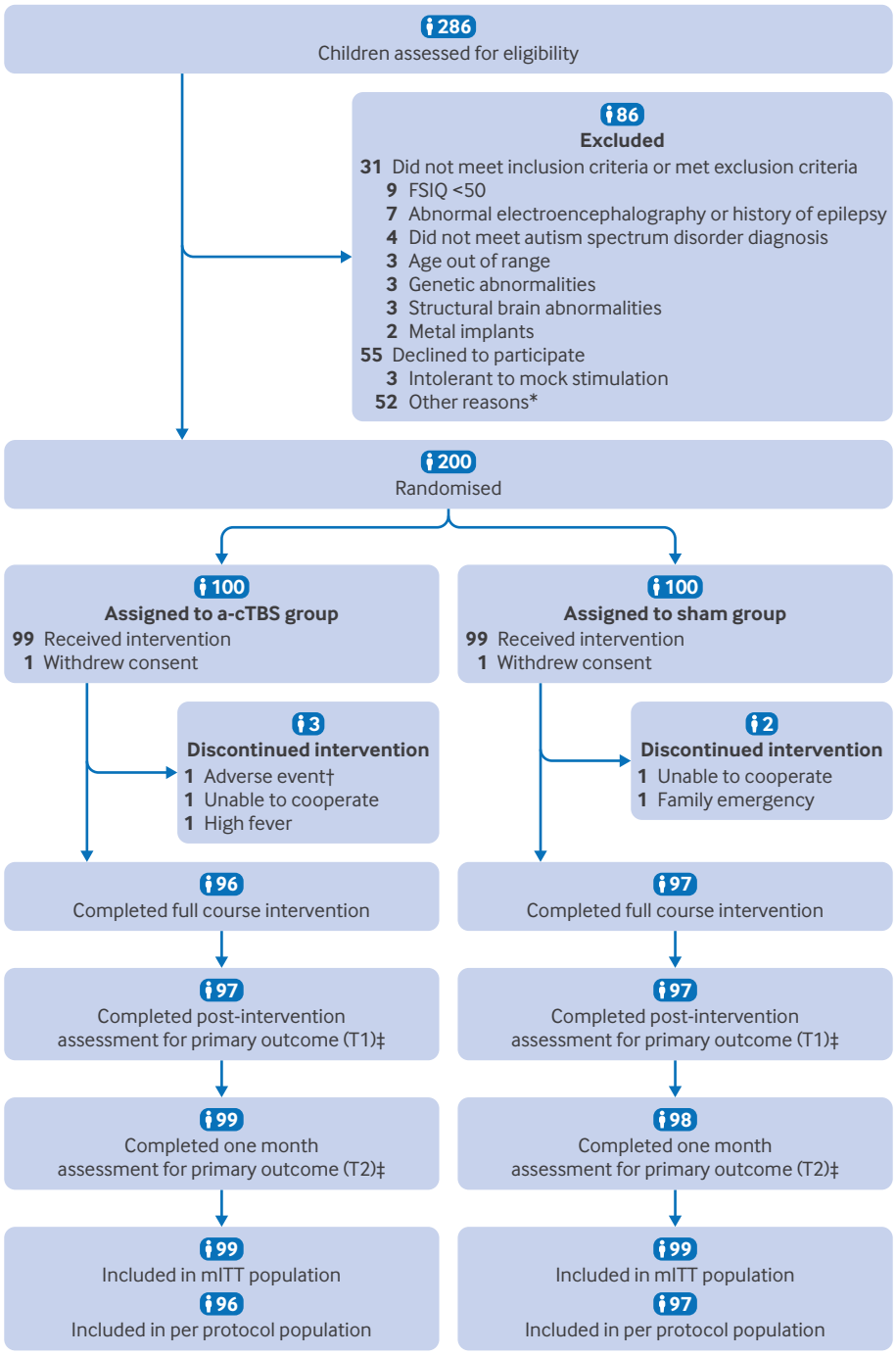


Fig 1 | Flow of participants through the study, including screening, randomisation, treatment allocation, withdrawals, and completion of T1 and T2 assessments. a-cTBS=accelerated continuous theta burst stimulation; FSIQ=full scale intelligence quotient; mITT=modified intention-to-treat population; T1=post-intervention; T2=one month follow-up. *Reasons for declining included concerns about safety or effectiveness of this new intervention, travel distance to study site, difficulty obtaining leave for five consecutive days, and undisclosed reasons. †One participant experienced a right upper limb spasm that resolved spontaneously. The stimulation was stopped and the symptom did not recur during follow-ups. This adverse event was classified as moderate. ‡All participants in the mITT population were successfully contacted and had at least completed evaluator interviews and safety assessments. At T1, two participants in each group (two active; two sham) did not complete the Social Responsiveness Scale, second edition; at T2, one participant in the sham group did not complete the assessment, despite repeated reminders. All declinations were owing to perceived time burden of follow-up scales. Details of missing outcomes are provided in supplementary methods

Secondary outcome measures

A-cTBS showed a significant treatment effect on the CGI-I scale, with 71.7% of participants in the active group reporting improvement compared with 46.5% in the sham group at T1 (P<0.001), and 84.8% versus 68.7% at T2 (P=0.008; supplementary figure S1, tables S6 and S7). Among the 119 participants (60.1%) with sufficient expressive language ability who completed the MAIN test, those in the a-cTBS group showed greater improvements in narrative production and

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Table 1 | Baseline characteristics of participants with autism spectrum disorder randomly assigned to receive active accelerated continuous theta burst stimulation or sham treatment

Characteristics	Active group (n=100)	Sham group (n=100)
Age (years), mean (SD)	6.6 (1.8)	6.4 (1.5)
Male	87 (87)	80 (80)
Residence		
Urban	92 (92)	96 (96)
Rural	8 (8)	4 (4)
IQ*		
Full scale IQ, mean (SD)	72.1 (18.8)	72.3 (16.9)
Comorbid with intellectual disability (full scale IQ <70)	50 (50)	51 (51)
Verbal IQ, mean (SD)	68.8 (19.1)	68.7 (16.6)
Performance IQ, mean (SD)	82.8 (17.5)	82.1 (19.4)
ADOS, mean (SD)†		
Communication	5.2 (1.8)	5.1 (1.6)
Social interaction	8.9 (2.4)	8.9 (2.3)
Social affect	14.1 (3.7)	14.0 (3.5)
Comorbid with ADHD	33 (33)	32 (32)
Concurrent psychotropic medication use‡	11 (11)	13 (13)
ADHD drug use (methylphenidate, tomoxetine)	11 (11)	10 (10)
ASD drug use (risperidone, aripiprazole)	7 (7)	9 (9)
Concurrent behavioural intervention‡	32 (32)	30 (30)
Site		
Shanghai	46 (46)	44 (44)
Shandong	34 (34)	36 (36)
Henan	20 (20)	20 (20)

Data are numbers (%) unless stated otherwise.
ADHD=attention deficit hyperactivity disorder; ADOS=Autism Diagnostic Observation Schedule; ASD=autism spectrum disorder; SD=standard deviation.
*IQ was assessed using age appropriate Wechsler scales: Wechsler Preschool and Primary Scale of Intelligence for children aged 4-6 years, and Wechsler Intelligence Scale-revised for those older than 6 years.
†Used to diagnose autism, with social affect scores comprising sum of communication and social interaction scores.
‡All participants who completed one month follow-up reported no changes in drugs or behavioural treatments during intervention and follow-up period.

comprehension (Cohen's d 0.12-0.47; all P<0.02; table 2). Active a-cTBS significantly improved all SRS-2 subscales except for restricted interests and repetitive behaviours at T1 and T2 (table 2; supplementary tables S1, S2, S9). No significant between group differences were observed for Vineland-3, CCDI, or PPVT scores (table 2). Improvement in SRS-2 was associated with an improvement in the Vineland-3 socialisation score (P<0.001; table S8).

Subgroup analyses

The treatment effect of a-cTBS remained consistent across subgroups (supplementary figure S2). Interaction tests showed no evidence of effect modification by intellectual disability status or age group at either follow-up visit (fig 2), addressing concerns about its efficacy in populations that were commonly underrepresented in ASD clinical trial research.

Safety and tolerability

Adverse events were more frequent in the active a-cTBS group than in the sham group (54.5% *v* 29.3%), with restlessness (39 *v* 21) and scalp discomfort (15 *v* 4) being the most common, respectively (table 3). Dizziness, poor sleep, and tinnitus occurred in less than 5% of participants. All adverse events were mild except for one moderate event; all resolved spontaneously. The moderate event was that one participant in the a-cTBS group experienced a right upper limb spasm during the fifth session on the last day of the intervention. The stimulation was stopped immediately. The child had no history of neurological disease and the symptom resolved spontaneously within minutes. Paediatric neurology evaluation recommended follow-up observation without drugs, and the symptom did not recur during follow-ups. Restlessness was the most common adverse event, which manifested as increased physical activity, talkativeness, and energy levels. This event typically emerged within hours after stimulation, persisted for hours to days, and was reported by parents as non-distressing without associated anxiety or functional impairment. No participants withdrew for this reason. Five participants did not complete the full course intervention (active n=3, sham n=2; fig 1). Apart from one moderate adverse event, the remaining reasons were non-cooperation, incidental high fever, or family scheduling constraints, which were unrelated to the stimulation.

Masking integrity

Masking was effective, with 82.8% (82/99) of caregivers in the active group and 72.7% (72/99) in the sham group believing their child received active treatment (P=0.09). Sensitivity analysis of expectancy effects revealed that actual treatment assignment significantly improved model fit compared with the base model, including only parental guess (P<0.001; supplementary table S10).

Discussion

Principal findings

This randomised controlled trial showed that a five day a-cTBS protocol targeting the left M1 significantly

Analysis population	No (active/ sham)	Adjusted mean difference (95% CI)	Cohen's d	P value	P for interaction
Post-intervention					
mITT	99 / 99	-6.25 (-8.69 to-3.81)	-0.92	<0.001	
Intellectual disability status					0.29
With intellectual disability	50 / 50	-6.43 (-10.13 to -2.73)	-1.38	<0.001	
Without intellectual disability	49 / 49	-5.71 (-8.98 to -2.44)	-1.21	0.001	
Age					0.63
4-6 years	45 / 44	-5.01 (-8.66 to -1.36)	-1.15	0.008	
6-10 years	54 / 55	-6.92 (-10.36 to -3.48)	-1.40	<0.001	
One month follow-up					
mITT	99 / 99	-6.17 (-8.65 to -3.70)	-0.90	<0.001	
Intellectual disability status					0.39
With intellectual disability	50 / 50	-7.46 (-11.11 to -3.80)	-1.55	<0.001	
Without intellectual disability	49 / 49	-4.98 (-8.39 to -1.56)	-1.05	0.005	
Age					0.91
4-6 years	45 / 44	-6.46 (-10.61 to -2.32)	-1.44	0.003	
6-10 years	54 / 55	-5.74 (-8.85 to -2.64)	-1.15	<0.001	

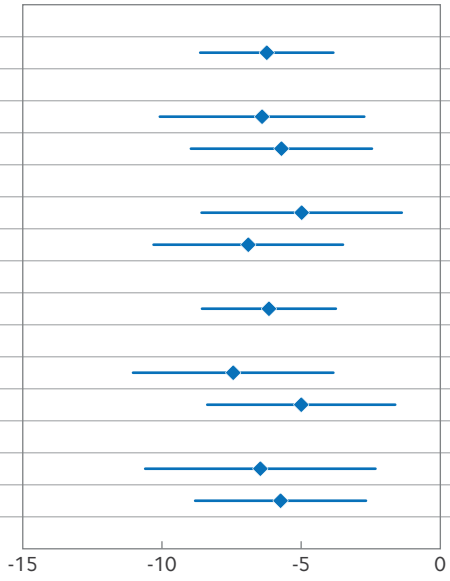

Fig 2 | Primary outcomes for a-cTBS group and sham group in mITT population and two key subgroups (intellectual disability status and age). Primary outcomes were SRS-2 total scores (range 0-195) at post-intervention and one month follow-up, with higher scores indicating greater severity of social communication impairment. Negative change from baseline indicates improvement. Analyses adjusted for comorbid with intellectual disability (yes or no), site, and baseline SRS-2 scores. a-cTBS=accelerated continuous theta burst stimulation; mITT=modified intention-to-treat population; SRS-2=Social Responsiveness Scale, second edition

improved social communication impairment in children with ASD. This stimulation also improved language abilities (measured by MAIN). The protocol proved extremely feasible, with high adherence rates (96% active, 97% sham). Safety profiles were favourable, with only mild to moderate adverse events typical of rTMS interventions. Our protocol showed feasibility and efficacy in young children and people with intellectual disability—populations traditionally underrepresented in neuromodulation studies.

Comparison with previous studies

Previous studies examining rTMS in improving social communication in people with ASD have reported inconsistent results.[10] One randomised trial (n=44) using an amygdala optimised, functional connectivity guided cTBS strategy targeting the left dorsolateral prefrontal cortex found improvements in social and communication skills in children with ASD who were minimally verbal.[15] However, the control group—who received non-optimised dorsolateral prefrontal cortex stimulation—also showed nominally significant, though less prominent, improvements in social outcomes. Additionally, the personalised targeting in this study required prolonged sedation and resting state functional magnetic resonance imaging, limiting clinical scalability. Four additional randomised controlled trials, mostly targeting the dorsolateral prefrontal cortex, involving adolescents and adults with ASD, showed only marginal or no benefit from rTMS.[11-14] These trials were limited by small sample sizes, single centre designs, requirement of neuronavigation, or exclusion of younger participants and those with intellectual disability. Our study used a new brain target and addressed these gaps through an rTMS protocol adapted for young children and children with intellectual disability. The comparable therapeutic outcomes observed in preschool aged children and those with intellectual disability support the broad applicability of the a-cTBS approach.

Clinical implications and rationale

In this study, the average treatment effects of a-cTBS exceeded the estimated MCID, suggesting its clinical importance. Two secondary outcomes assessed by evaluators masked to the intervention further validated the clinical relevance. Firstly, the CGI-I analysis showed a significant treatment effect, with 71.7% of participants in the active group reporting improvement compared with only 46.5% in the sham group at post-intervention (P<0.001), and 84.8% versus 68.7% at the one month follow-up (P=0.008). Secondly, the MAIN assessment, a standardised tool for evaluating narrative competence, revealed significant improvements in narrative skills (Cohen's d=0.47, P<0.001). These results collectively indicated a clinically important treatment effect of a-cTBS. Our estimation of MCID represents only a preliminary post hoc reference value. Larger scale validation studies are needed to establish an MCID on SRS-2.

The safety profile observed in this trial was favourable, with only one adverse event graded as moderate and all the remaining events mild. Only one discontinuation was related to adverse events relevant

Table 2 | Secondary outcomes for active accelerated continuous theta burst stimulation group and sham group in modified intention-to-treat population at one month follow-up

Outcome	Baseline		One month follow-up		Adjusted mean difference (95% CI)*	Cohen's d	P value
	Active group	Sham group	Active group	Sham group			
Vineland-3†	n=99	n=99	n=99	n=99	—	—	—
Adaptive behaviour composite	78.22 (11.18)	81.26 (12.11)	82.54 (13.40)	83.40 (13.34)	1.74 (−0.97 to 4.45)	0.31	0.21
Communication	81.28 (15.09)	85.27 (13.28)	86.53 (16.92)	88.45 (17.00)	1.57 (−1.99 to 5.13)	0.30	0.38
Daily living skills	83.19 (13.09)	86.02 (13.40)	87.02 (14.22)	87.95 (13.99)	1.15 (−1.99 to 4.29)	0.21	0.47
Socialisation	74.54 (14.69)	77.21 (14.44)	78.32 (15.57)	78.25 (14.46)	2.18 (−0.74 to 5.10)	0.36	0.14
MAIN‡	n=56	n=63	n=56	n=63	—	—	—
Production							
Tell story	10.54 (4.51)	11.95 (4.87)	12.09 (4.62)	11.33 (4.56)	1.86 (0.73 to 2.98)	0.35	0.001
Retell story	14.91 (5.22)	16.25 (5.16)	17.45 (4.97)	15.94 (4.82)	2.46 (1.48 to 3.45)	0.47	<0.001
Comprehension							
Tell story	5.04 (2.78)	5.63 (2.76)	7.08 (2.78)	6.28 (2.60)	1.21 (0.53 to 1.89)	0.24	<0.001
Retell story	7.25 (2.08)	7.62 (1.97)	8.25 (1.72)	7.83 (1.91)	0.62 (0.13 to 1.10)	0.12	0.01
PPVT§	n=99	n=99	n=99	n=99	—	—	—
Raw score	52.02 (28.25)	50.85 (26.18)	59.88 (27.55)	56.51 (25.34)	2.27 (−0.40 to 4.94)	0.33	0.10
PPVT IQ (n=84 *v* 91)	85.12 (25.92)	85.69 (23.21)	93.57 (27.21)	91.38 (22.92)	2.59 (−1.10 to 6.28)	0.40	0.17
CCDI¶	n=55	n=58	n=55	n=58	—	—	—
Words produced, median (IQR)	753.0 (697.0-787.0)	731.5 (691.3-775.5)	764.0 (718.5-797.0)	766.5 (717.7-789.2)	−1.96 (−15.43 to 11.52)	−0.38	0.77
Sentence complexity, median (IQR)	63.0 (48.5-74.0)	65.5 (51.0-73.0)	68.0 (59.0-77.0)	69.0 (59.3-75.6)	−0.10 (−3.02 to 2.82)	−0.02	0.95
SRS-2 subscales	n=99	n=99	n=99	n=99	—	—	—
Social awareness	12.53 (3.03)	11.61 (3.04)	11.00 (2.86)	10.89 (2.86)	−0.48 (−1.09 to 0.13)	−0.07	0.12
Social cognition	17.28 (4.45)	16.38 (4.31)	14.33 (4.02)	14.76 (4.30)	−1.07 (−1.80 to −0.34)	−0.16	0.004
Social communication	29.84 (7.92)	27.08 (7.53)	24.75 (7.78)	24.73 (7.62)	−2.37 (−3.52 to −1.22)	−0.35	<0.001
Social motivation	12.64 (4.89)	12.20 (4.58)	10.75 (4.64)	11.38 (4.47)	−0.99 (−1.73 to −0.26)	−0.14	0.009
Restricted interests and repetitive behaviours	12.00 (5.12)	11.58 (5.56)	10.56 (5.38)	10.85 (5.10)	−0.63 (−1.40 to 0.14)	−0.09	0.11

Data are means (standard deviations) unless stated otherwise.
CCDI=Chinese Communicative Development Inventory; IQR=interquartile range; MAIN=Multilingual Assessment Instrument for Narratives; PPVT=Peabody Picture Vocabulary Test; SRS-2=Social Responsiveness Scale, second edition; Vineland-3=Vineland Adaptive Behaviour Scale, third edition.
*Adjusted for comorbid with intellectual disability (yes or no), site, and baseline score for each outcome. Score changes indicated improvement in opposite directions (negative for SRS-2, positive for Vineland-3, MAIN, PPVT, and CCDI).
†Measures adaptive functioning across domains. Scores standardised with normative mean of 100 and standard deviation of 15 for composite and domain scores.
‡Measures narrative comprehension and production skills, with higher scores indicating higher narrative skills. MAIN test requires sufficient expressive language skills and compliance. All excluded participants (n=79) were ineligible owing to limited language expression or poor cooperation.
§Measures single word comprehension, with higher scores indicating better abilities. PPVT raw scores were collected for all participants. For children ≤8.5 years, scores were normalised to an IQ scale with mean of 100 and standard deviation of 15. For children >8.5 years, only raw scores were used owing to unavailability of age adjusted IQ norms for this age group.
¶Measures language development, with higher scores indicating better language abilities. Children who reached the maximum CCDI score at baseline (ceiling effect) had no room for improvement and were excluded from CCDI administration at follow-up. CCDI changes appeared to follow normal distribution, therefore between-group differences in means were analysed using linear regression.

to the intervention. Restlessness and scalp discomfort were more prevalent in the intervention group but resolved spontaneously, consistent with the pattern of adverse events observed in previous studies.[28 58-60] These adverse events were comprehensively assessed across several sources, given the challenges of assessing subjective experiences in children with communication difficulties.

This study highlighted the therapeutic potential of targeting M1 for ASD. While atypical neurophysiological responses to transcranial magnetic stimulation at the left M1 have previously been reported in people with ASD,[9 23-25] this region has not been specifically targeted in therapeutic interventions for ASD. M1 is increasingly recognised for its roles beyond motor control,[20 61] including involvement in semantic processing,[62] language function, and social cognition.[21 22] M1 also connects to emotion processing regions, including the occipito-temporal regions, the amygdala, pulvinar cortex, and orbitofrontal cortex.[63 64] From a practical standpoint, M1 can be precisely localised by motor evoked potential, enabling consistent targeting without the need for neuronavigation systems. This approach addressed the compliance challenges in young children with ASD, particularly those with intellectual disability. Furthermore, the need for expensive neuronavigation equipment and specialised professionals is eliminated, therefore improving scalability.

Our protocol was specifically designed to optimise treatment adherence and efficacy. cTBS, a more time efficient variant of rTMS, reduces the standard 20 min stimulation session to several 40 s sessions. The condensed five day course further reduces the conventional treatment duration from weeks or months to just five days without compromising therapeutic efficacy.[10 65] Both modifications produced comparable or superior efficacy compared with traditional rTMS through cumulative synaptic strengthening.[27 28] The protocol achieved a high adherence rate, with 193 out of 200 (96.5%) enrolled participants completing all sessions.

Consistent with our earlier pilot study, our a-cTBS protocol targeting the left M1 specifically

Table 3 | Adverse events in participants receiving at least one active accelerated continuous theta burst stimulation or sham treatment

Adverse event	Active group (n=99)	Sham group (n=99)	P value
Restlessness	39 (39.4)	21 (21.2)	0.005
Scalp discomfort	15 (15.2)	4 (4.0)	0.01
Dizziness	4 (4.0)	2 (2.0)	0.68
Poor sleep	1 (1.0)	2 (2.0)	>0.99
Tinnitus	0 (0)	2 (0)	0.50
Transient limb spasm	1 (1.0)*	0 (0)	>0.99

Data are numbers (%).
*One participant experienced a right upper limb spasm during fifth session on last day of intervention. The stimulation was terminated immediately and the symptom resolved spontaneously within minutes. Paediatric neurology evaluation recommended follow-up observation without drugs, and the symptom did not recur during follow-ups. This event was classified as moderate.

improved social communication impairment but did not significantly affect restrictive and repetitive behaviours—another core symptom of ASD.[19] This pattern aligns with established neural circuitry models. Restrictive and repetitive behaviours are predominantly associated with the cortico-striatal-thalamo-cortical and cerebellar circuits, which have limited direct connectivity with M1.[66 67] The intervention led to broader functional gains in language abilities. The observed improvements aligned with reductions in SRS-2 scores at follow-up. The concurrent improvements observed across social communication and language domains suggest robust treatment effects that may reflect shared underlying mechanisms. For instance, enhanced language abilities may support better social communication abilities. Also, we cannot rule out the possibility that the motor system serves as a hub connecting action understanding, language processing, and social interaction.[68] Future studies are warranted to investigate the underlying mechanisms.

Strengths and limitations

This study has several important strengths. The trial included two key autism subpopulations that were frequently excluded from rTMS studies: children with intellectual disability and children of young age. Approximately 33% of people with ASD also experience intellectual disability, representing a population with important intervention needs. Despite their substantial treatment requirements, these people are frequently excluded from many clinical trials.[3 69] For children of young age, the focus is particularly important because this developmental period is characterised by heightened neuroplasticity, which may increase the efficacy of therapeutic intervention.[70] The consistent treatment effects across these subgroups support the protocol's broad applicability. Furthermore, the protocol's simplicity is an advantage, featuring brief sessions and no requirement for neuronavigation. These characteristics make the procedure more widely suitable for many clinical care settings and patient groups. Nonetheless, the costs of transcranial magnetic stimulation devices are still prohibitive in low resource settings. Further innovations are needed to improve affordability and accessibility.

Several limitations warrant consideration when interpreting the results. Although we anticipated equivalent groups owing to randomisation, we observed a trend towards baseline differences in SRS-2 scores between groups. While the SRS-2 is a widely used and well validated parent reported measure, variability across raters is a recognised limitation. Our sensitivity analyses showed consistent treatment effects, and within-person changes might be more clinically meaningful, although we cannot completely rule out the influence of these initial differences on our findings.

Ratings of SRS-2 may reflect domains beyond social impairment, including behaviour regulation, attention, and cognitive level. Additionally, contextual variability and rater characteristics—including manifestations of the broad autism phenotype in some caregivers—may influence scoring. Although our one month follow-up aligned with the time frame used in previous rTMS studies in depression and ASD,[29] longer term follow-up (six months or longer) is needed to evaluate the durability of effects.

We also observed a trend towards greater treatment expectancy in the intervention group, which may have introduced expectancy bias.[71] This observation likely reflects differential adverse effect profiles between groups. Although randomisation should have balanced baseline expectations, we did not collect pretreatment data to confirm this. Sensitivity analyses and effects observed on masked evaluator rated measures (CGI-I and MAIN) partially mitigate this concern; however, expectancy effects may have contributed to the magnitude of the estimated treatment benefit, and this possibility should be considered when interpreting these findings.

Finally, more than 80% of enrolled participants were boys, consistent with typical ASD prevalence patterns but limiting its generalisability to girls. While sex stratified analyses revealed directionally similar treatment effects between male and female participants, the limited number of female participants precluded definitive conclusions about sex specific responses.

Future studies should focus on including children with ASD from families of different socioeconomic statuses and considering barriers to accessing interventions. Understanding the practical challenges faced by underserved families will be essential for improving accessibility and ensuring equitable

implementation. Additionally, future work should extend beyond symptom reduction to evaluate real world and functional outcomes across diverse socioeconomic contexts. This approach should include broader measures such as healthcare use, behavioural functioning in everyday settings, and caregiver stress. Such comprehensive evaluation would help quantify the true public health relevance of the intervention and its broader impact on children with ASD and their families.

Conclusions

The five day a-cTBS protocol targeting the left M1 provides a feasible, effective, and scalable therapeutic option for children with ASD, including those with intellectual disability. By addressing key limitations of conventional rTMS, this protocol represents a major advancement towards equitable autism care worldwide.

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Data sharing: The code used to analyse the data in the paper can be found in the supplementary appendix. The data underlying the findings in this paper are openly and publicly available and can be found at: https://osf.io/tg9me/overview. If problems are encountered accessing the data, please contact the corresponding author.

Transparency: The manuscript's guarantor (FL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as registered have been explained.

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Web appendix 1: Supplementary appendix
Web appendix 2: Protocol and statistical analysis plan