

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

**Supplementary Data**

**Table of Contents**

sMethods. Inclusion and Exclusion Criteria	3
sMethods. Sample size calculation	4
sMethods. a-cTBS intervention	5
Figure S1. Flow chart of the a-cTBS clinical trial.	6
Figure S2. The schematic representation of the a-cTBS target, the left M1.	7
Figure S3. Accelerated continuous theta-burst stimulation protocol.	8
Figure S4. The change in SRS subscale scores from baseline to the 1-month follow-up in a-cTBS and historic control groups.	10
Table S1. Demographic and clinical characteristics of the a-cTBS participants at the baseline.	11
Table S2. Characteristics of the participants of the clinical trial and historical controls that were eligible for comparison before and after IPTW.	12
Table S3. The association between a-cTBS and 1-month changes in SRS scores comparing participants in the clinical trial with historic controls.	13
Table S4. Additional analyses for 1-month changes in SRS scores	14
Table S5. Improvements of 30 participants as reported by their caregivers at 1-month follow-up.	15
Table S6. The correlation between baseline characteristics and $\Delta\text{SRS}_{1\text{mon}}$ .	20
sReference	21



**sMethods. Inclusion and Exclusion criteria**

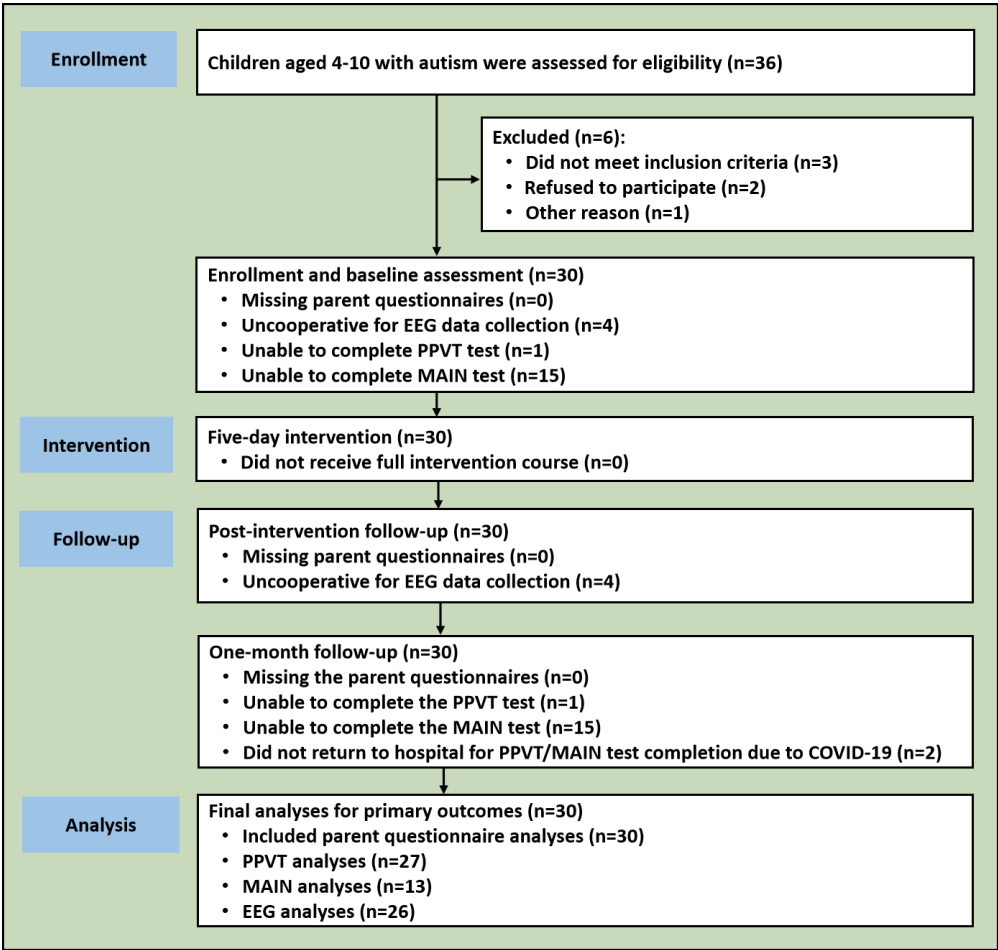
Eligible participants were children aged 4 to 10 with a diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Edition 5, and further confirmed by the Autism Diagnostic Observation Schedule. We excluded patients if they had metal in the head or neck, a history of epilepsy or other neurological diseases, structural brain abnormalities requiring surgical treatment, as indicated by magnetic resonance imaging (MRI), confirmation of genetic or chromosomal abnormalities, a diagnosis of psychiatric disorders other than ASD (e.g., very early-onset schizophrenia), or severe heart disease and/or hearing impairment. Patients who received other new interventions or treatments within 4 weeks prior to enrollment or who were currently participating in other clinical trials were also excluded. Notably, participants with cooccurring attention-deficit hyperactivity disorder (ADHD) were included because ADHD is the most common co-occurring condition of ASD; moreover, it might have a similar neurodevelopmental nature and share some etiologies with ASD. All psychotropic medications were continued without change during the trial.

**sMethods. Sample size calculation**

The total sample size was estimated using G\*Power, which showed that 30 participants would provide enough power (80% power and two-sided 5% significance) to detect a moderate-to-large standardized effect of treatment, considering a 10% dropout rate. The estimated effect size was guided by existing results on social behavior deficits (Barahona-Correa et al., 2018; Ni et al., 2021).

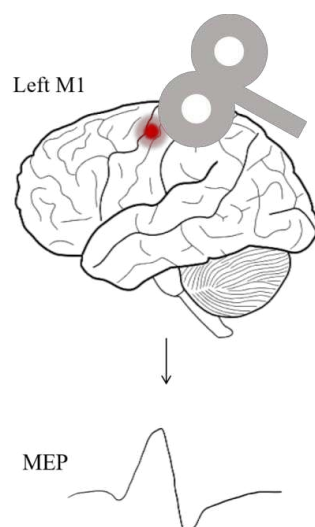
**sMethods. a-cTBS intervention**

In the trial, we used two pulsed magnetic stimulation devices (M-100 Ultimate, Shenzhen Yingchi Technology Co., Ltd., Shenzhen, China). A professionally trained physician was responsible for locating the target position, the left M1 ('motor hot spot'), where stimuli of intensity slightly above the resting motor threshold (RMT) could consistently produce the largest motor evoked potential (MEP) in the right abductor pollicis brevis muscle (Figure S2). The resting motor threshold was defined as the lowest TMS intensity needed to elicit a MEP of more than 50 $\mu$ V in at least 5 out of 10 stimuli recorded in the corresponding muscle (Schutter & van Honk, 2006). During stimulation, children were instructed to sit on a chair and keep their heads still (with their parents' assistance, when needed). The coil was held tangentially over the left M1, and the handle of the coil was pointed backward at 45° from the mid-sagittal line. The stimulus intensity was set to 80% RMT. The detailed a-cTBS protocol was as follows: 60 cycles of 10 bursts of 3 pulses at 50 Hz were delivered in 2-second trains (5 Hz) with no intertrain interval (i.e., triplet standard cTBS, 1800 pulses, 120 seconds). Stimulation sessions were delivered hourly, and 10 sessions were performed per day (18,000 pulses/day) for 5 consecutive days (90,000 pulses in total; Figure S3).



**Figure S1. Flow chart of the a-cTBS clinical trial.**

Abbreviations: EEG, electroencephalogram; PPVT, the Peabody Picture Vocabulary Test; MAIN, the Multilingual Assessment Instrument for Narratives; a-cTBS, accelerated continuous theta-burst stimulation.



**Figure S2. The schematic representation of the a-cTBS target, the left M1.**

Abbreviation: M1, primary motor cortex; MEP, motor-evoked potential.

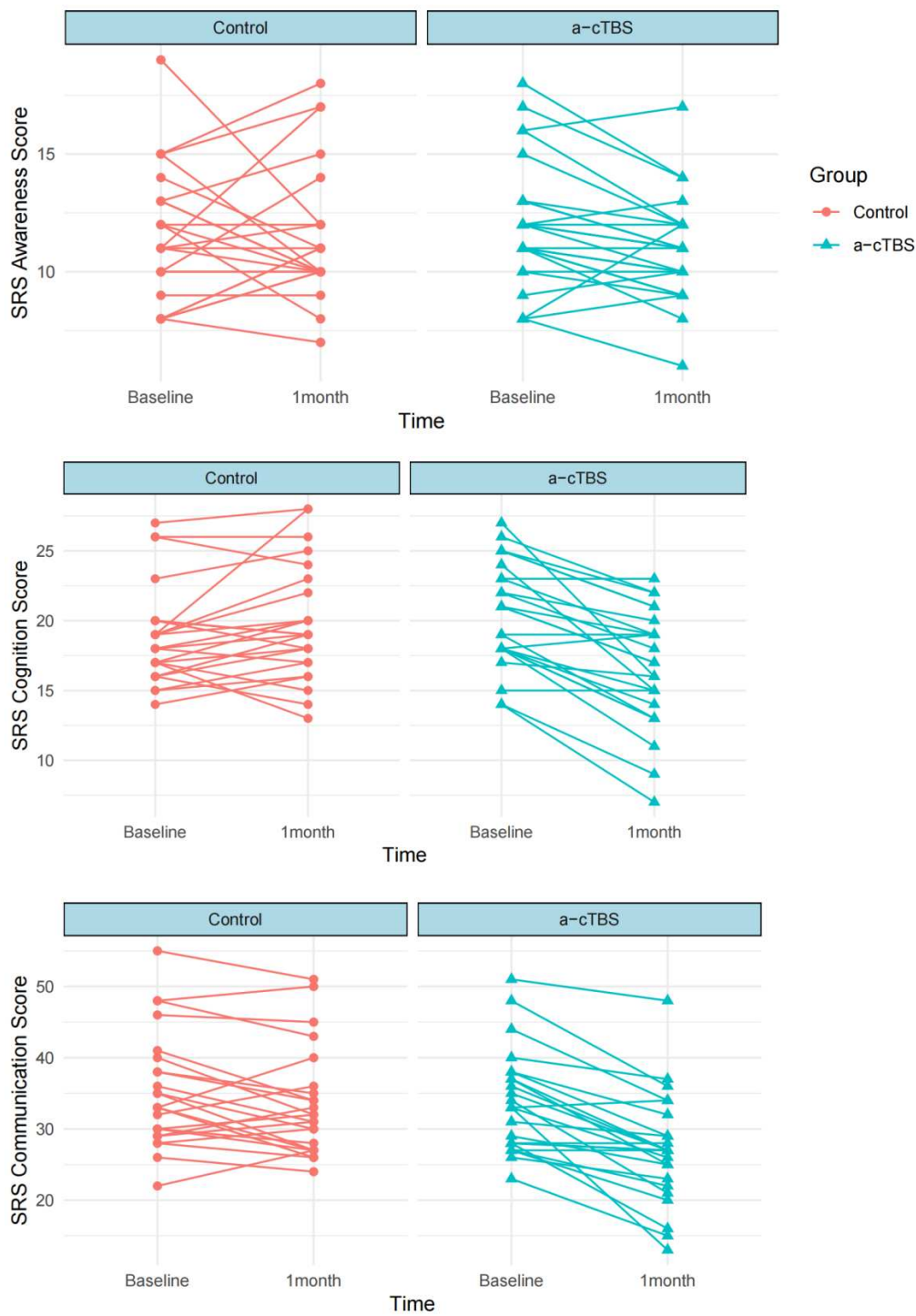
Day1	Day2	Day3	Day4	Day5
cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800
50-60 min ISI	50-60 min ISI	50-60 min ISI	50-60 min ISI	50-60 min ISI
cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800
50-60 min ISI	50-60 min ISI	50-60 min ISI	50-60 min ISI	50-60 min ISI
cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800	cTBS 1800
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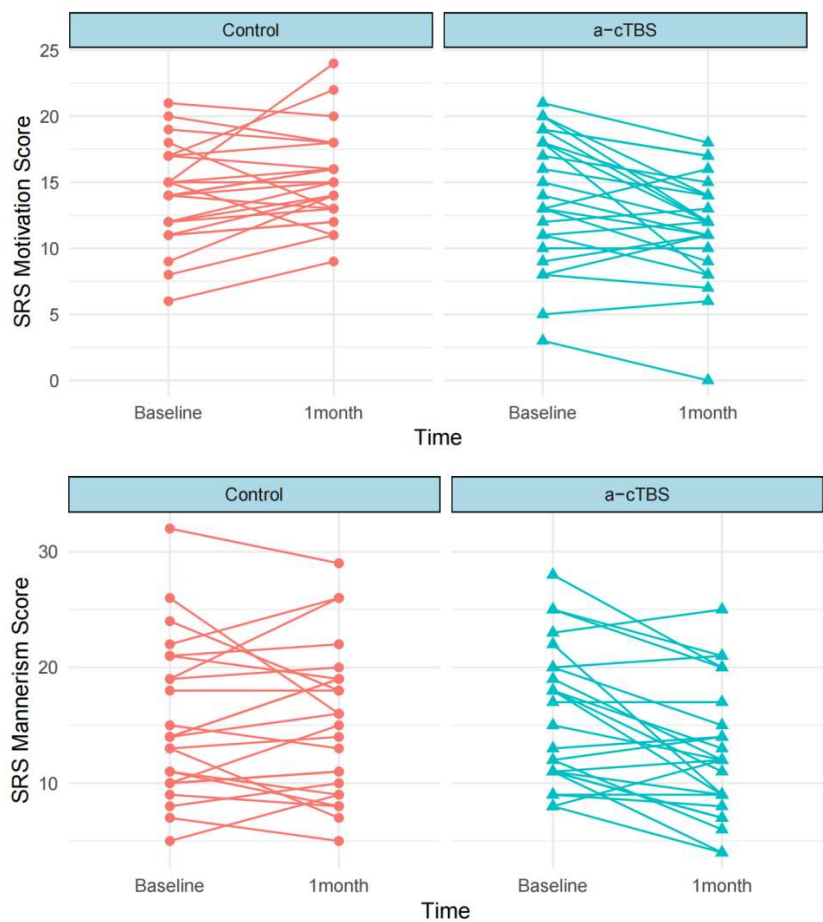
**Figure S3. Accelerated continuous theta-burst stimulation protocol.**

Abbreviations: cTBS, continuous theta-burst stimulation; ISI, intersession interval.

\* 10 sessions per day of 1,800 pulses per session for a total of 18,000 pulses per day.







**Figure S4. The change in SRS subscales scores score from baseline to the 1-month follow-up in a-cTBS and historic control groups.**

Abbreviation: a-cTBS, accelerated continuous theta-burst stimulation; SRS, social responsiveness scale.

**Table S1. Demographic and clinical characteristics of the a-cTBS participants at the baseline.**

	a-cTBS (n=30)
Age (years)	7.06 (1.55)
Gender (male/female)	24/6
FSIQ	74.97 (24.70)
CARS	33.48 (2.59)
ADOS	
Communication	4.70 (1.24)
Social Interaction	9.03 (1.81)
SA_Total score	13.73 (2.74)

Data are presented as mean (SD) for continuous variables.  
Abbreviations: FSIQ = full-scale IQ, CARS = Childhood Autism Rating Scale, ADOS = Autism Diagnostic Observation Schedule, SA\_Total score = ADOS\_Communication score + ADOS\_Social Interaction score.

**Table S2. Characteristics of the participants of the clinical trial and historical controls that were eligible for comparison before and after IPTW.**

	Before IPTW			After IPTW		
	a-cTBS (n=25.00)	Control (n=24.00)	SMD	a-cTBS (n=22.97)	Control (n=18.85)	SMD
Age, years *	6.57 (1.10)	5.67 (1.36)	0.73	6.38 (1.04)	6.24 (1.41)	0.12
Male *	20.00 (80.0)	19.00 (79.2)	-0.01	18.12 (78.80)	15.28 (81.05)	0.02
FSIQ *	73.84 (24.19)	58.25 (16.69)	0.75	68.00 (23.38)	65.64 (19.30)	0.11
CARS *	33.76 (2.43)	35.27 (3.29)	-0.52	34.10 (2.43)	34.27 (3.24)	-0.06
Period between baseline and 1-month follow-up, days	40.20 (4.42)	36.42 (6.43)	0.69	40.18 (4.38)	36.58 (6.44)	0.65

Data are presented as No. (%) for categorical variables and mean (SD) for continuous variables.

Abbreviation: IPTW, inverse probability of treatment weighting; a-cTBS, accelerated continuous theta-burst stimulation; SMD, standardized mean difference; SD, standard deviation; FSIQ, full-scale IQ; CARS, Childhood Autism Rating Scale.

\* Involved in the IPTW.

**Table S3. The association between a-cTBS and 1-month changes in SRS scores comparing participants in the clinical trial with historic controls.**

	N	Crude $\beta$ (95% CI)	Weighted $\beta^*$ (95% CI)
<b>SRS total score</b>	49		
a-cTBS $\times$ Time <sup>†</sup>		-17.53 (-23.56, -11.51)	-17.44 (-20.06, -14.99)
Time		0.29 (-4.01, 4.60)	0.75 (-0.88, 2.48)
a-cTBS		1.01 (-10.41, 12.43)	0.71 (-3.82, 5.40)
<b>SRS subscales scores</b>			
<b>Social awareness</b>	49		
a-cTBS $\times$ Time		-1.04 (-2.49, 0.41)	-1.26 (-1.87, -0.64)
Time		-0.04 (-1.08, 0.99)	0.29 (-0.29, 0.84)
a-cTBS		0.50 (-1.02, 2.02)	0.54 (-0.08, 1.19)
<b>Social cognition</b>	49		
a-cTBS $\times$ Time		-4.80 (-6.38, -3.22)	-5.02 (-5.69, -4.30)
Time		0.92 (-0.21, 2.04)	1.07 (0.69, 1.44)
a-cTBS		1.61 (-0.63, 3.84)	1.61 (0.79, 2.47)
<b>Social communication</b>	49		
a-cTBS $\times$ Time		-4.73 (-7.46, -1.99)	-4.14 (-5.29, -2.98)
Time		-1.83 (-3.79, 0.12)	-2.08 (-2.93, -1.30)
a-cTBS		-1.57 (-5.88, 2.75)	-2.03 (-3.69, -0.33)
<b>Social motivation</b>	49		
a-cTBS $\times$ Time		-3.57 (-5.38, -1.76)	-3.45 (-4.19, -2.70)
Time		1.17 (-0.13, 2.46)	1.12 (0.54, 1.68)
a-cTBS		-0.04 (-2.40, 2.31)	-0.15 (-1.10, 0.82)
<b>Autistic mannerism</b>	49		
a-cTBS $\times$ Time		-3.40 (-5.74, -1.07)	-3.56 (-4.50, -2.60)
Time		0.08 (-1.59, 1.75)	0.34 (-0.30, 0.93)
a-cTBS		0.51 (-3.04, 4.06)	0.53 (-0.90, 2.04)

Abbreviation: a-cTBS, accelerated continuous theta-burst stimulation; SRS, social responsiveness scale; CI, confidence intervals.

\* The propensity score for IPTW was estimated with sex, age at baseline, full-scale IQ, and Childhood Autism Rating Scale score.

<sup>†</sup> The treatment effect of a-cTBS was assessed by the interaction term a-cTBS (0 for control, 1 for treatment) $\times$ Time (0 for pretreatment, 1 for 1-month follow-up). We also present the coefficients of Time, which indicate the average longitudinal change of SRS in both groups. The coefficients of a-cTBS represent the mean difference between the two groups before treatment.

**Table S4. Additional analyses for 1-month changes in SRS scores**

	Crude $\beta$ (95% CI)	Weighted $\beta^*$ (95% CI)
<b>SRS total score</b>		
Mixed model, continuous time (days after baseline assessment)		
a-cTBS $\times$ Time (days)	-0.42 (-0.58, -0.26)	-0.42 (-0.48, -0.36)
Time (days)	0.001 (-0.12, 0.12)	0.01 (-0.03, 0.05)
a-cTBS	0.71 (-10.72, 12.14)	0.37 (-4.16, 5.06)
Linear model (adjusted for the SRS total score at baseline)		
a-cTBS	-17.36 (-23.14, -11.59)	-17.02 (-22.96, -11.47)
SRS at baseline	0.83 (0.69, 0.98)	0.85 (0.72, 1.00)

\*The propensity score for IPTW was estimated with sex, age at baseline, IQ, and Childhood Autism Rating Scale score.

Abbreviation: a-cTBS, accelerated continuous theta-burst stimulation; SRS, social responsiveness scale; CI, confidence intervals.

**Table S5. Improvements of 30 participants as reported by their caregivers at 1-month follow-up.**

No.	1-month improvement summary from caregivers			
	Social	Language	Behaviors and Emotions	CGI-I
1	Understanding relationships better; e.g., parents could negotiate with him to do something.	NA	Control emotions better; Not so stubborn like before; Had some improvement on executive ability such as homework.	3
2	Social initiative and eye contact with parents had increased;	Vocabulary had grown; The complexity and logic of speech had enhanced; e.g., before “I want to drink water”, after treatment “I am thirsty so I want some water”	Not so stubborn like before;	3
3	Normal back-and-forth conversation had increased; Could more clearly put forward his requirements	Vocabulary had grown; The complexity and logic of sentences had enhanced	Control emotions better;	3
4	Eye contact with mother had increased; Occasionally respond to mom’s saying;	Vocabulary had grown a little;	NA	4
5	Eye contact with family members had increased;	Vocabulary had grown (but a large part is self-talking)	Not so stubborn like before; could do things according to instructions in most cases;	3
6	Social initiative had increased; parents and teachers felt he was more sensible;	Vocabulary had grown a little; willing to respond with more long sentences (previously, always answer	Control emotions better; more willing to do things according to instructions both at home and school;	3

		“I don’t know”);	Sleep better;	
7	Social initiative had increased greatly; she became to enjoy school life and made some friends;	The complexity and logic of speech had enhanced a lot (can use some adjectives to modify sentences).	Control emotions better; Not so stubborn like before; Motivation to do things had increased.	2
8	Social initiative had increased (willing to start a conversation with family and answer more)	The complexity and logic of speech had enhanced; Sometimes he could tell a story completely;	Not so stubborn like before; had some improvement on executive ability especially in school.	3
9	Social initiative had increased, e.g., actively talk about what happened at school.; irrelevant answer had decreased.	Say more; The complexity and logic of speech had enhanced a lot;	Control emotions much better	2
10	Social initiative had increased; cared about people around him; but couldn’t handle the right social distance.	The complexity and logic of sentences had enhanced;	NA	3
11	Social initiative had increased a little;	Say more;	NA	3
12	Social initiative had increased; cared about people around him (e.g., give up his seat on the subway);	communication topics had become more and logic of speech had improved	NA	3
13	Social initiative with peers had increased (e.g., initiate a chat); irrelevant answer had decreased.	Stereotyped language had decreased.	Procrastination had improved especially when doing homework.	3



14	Had some improvement in recognizing emotions/thoughts of others.	NA	NA	3
15	Began to have competitive thoughts (He cares if his classmates get better grades than him)	NA	Had some improvement on executive ability (could made an agreement with parents and follow it; made a plan for his homework)	3
16	Eye contact with family members had increased; some occasional pertinent answer surprised his mother; began to notice and care people around.	Vocabulary had grown a little.	Not so stubborn like before (especially sensory aspect: don't resist haircuts and hats)	3
17	NA	NA	Teachers felt he was more obedient than last semester, e.g., obey the rules, take notes in class.	3
18	Social initiative had increased (spend more time playing with his peers)	Talk more; communication topics had become richer; the complexity and logic of speech had enhanced.	NA	3
19	Social initiative had increased a lot (e.g., say hello actively, ask about grandpa's health condition)	NA	Not so stubborn like before; willing to try to do more things; could control his emotion better.	2
20	Say hello actively; appeared to be shy at certain condition.	The complexity of sentences had enhanced a little;	The logical understanding of mathematical questions has improved;	3
21	Social initiative had	Vocabulary had grown;	NA	3

	increased (e.g., took the initiative to talk about what happened in the kindergarten, liked playing with children, not limited to chasing games); liked parents’ and teachers’ attention and praise	Talk more; communication topics had become richer; the complexity of speech had enhanced.		
22	NA (The mother did not describe the child's changes due to recent business trip).	Language comprehension had improved a little;	Teacher said he performed well at class	3
23	Social initiative had increased a lot (e.g., took the initiative to talk about what happened in the school and the stories she had read). Chat with mom longer and deeper.	The complexity and logic of speech had enhanced.	Willing to discuss with parents in advance; had some improvement on executive ability (e.g., doing homework)	2
24	NA	NA	Had some improvement on executive ability; could control his emotion better.	3
25	NA	Language comprehension had improved a little;	Not so stubborn like before;	3
26	Social initiative had increased a lot (e.g., “ I want to go out to play with kids”, play imaginary games; took the initiative to share the cartoon stories with	The complexity and logic of sentences had enhanced.	NA	2

		mom).		
27	NA	Vocabulary had grown (parents think the improvement may be due to their storytelling training at home)	Not so stubborn like before	3
28	NA	NA	NA	4
29	NA	NA	NA	4
30	Empathize ability had improved (e.g., “Dad, be quiet, Mom is having a rest.”); took the initiative to introduce his classmates with parents.	Vocabulary had grown; the complexity and logic of speech had enhanced (could use more descriptive words).	NA	3

Abbreviation: CGI-I, the Clinical Global Impression of Improvement, a seven-point scale: 1 = “very much improved” to 7 = “very much worse”; NA, not applicable.

**Table S6. The correlation between baseline characteristics and  $\Delta$ SRS<sub>1mon</sub>.**

Characteristics	N	Correlation between baseline characteristics and $\Delta$ SRS <sub>1mon</sub>	
		Crude $\beta$ (95% CI)	Adjusted $\beta$ (95% CI) *
Age	30	1.10 (-1.63, 3.83)	1.06 (-1.62, 3.73)
Sex	30	2.83 (-7.63, 13.30)	4.76 (-5.62, 15.13)
CARS	30	-0.31 (-1.96, 1.33)	0.97 (-1.21, 3.15)
ADOS_SA	30	0.28 (-1.28, 1.84)	1.37 (-0.40, 3.14)
VIQ	30	0.15 (-0.02, 0.31)	0.12 (-0.05, 0.29)
PIQ	30	0.05 (-0.12, 0.22)	0.02 (-0.15, 0.20)
FSIQ	30	0.12 (-0.05, 0.28)	0.09 (-0.08, 0.26)
PPVT_raw score	29	0.03 (-0.13, 0.19)	0.02 (-0.14, 0.18)
PPVT_IQ	29	0.03 (-0.12, 0.18)	0.02 (-0.13, 0.18)
CCDI_Words produced	30	0.02 (-0.01, 0.05)	0.01 (-0.03, 0.05)
CCDI_Sentence complexity	30	0.05 (-0.17, 0.27)	-0.05 (-0.29, 0.20)

\* Adjusted for the baseline SRS total score.  
Abbreviations: SRS, Social Responsiveness Scale; CARS, Childhood Autism Rating Scale; ADOS, Autism Diagnostic Observation Schedule; VIQ, verbal IQ; PIQ, performance IQ; FSIQ, full-scale IQ; CCDI, Chinese Communicative Development Inventory; PPVT, Peabody Picture Vocabulary Test; MAIN, Multilingual Assessment Instrument for Narratives;  $\Delta$ SRS<sub>1mon</sub>, SRS<sub>1mon</sub> - SRS<sub>base</sub>; CI, confidence intervals.

## sReference

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