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Original Article

5-day multi-session intermittent theta burst stimulation over bilateral posterior superior temporal sulci in adults with autism-a pilot study

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ABSTRACT

Background: Theta burst stimulation (TBS), a patterned repetitive transcranial magnetic stimulation (rTMS) protocol with shorter simulation duration and lower stimulus intensity, could be a better protocol for individuals with autism spectrum disorder (ASD). Our study aimed to explore the impacts of intermittent TBS (iTBS) over the bilateral posterior superior temporal sulcus (pSTS) on intellectually able adults with ASD.

Methods: In this randomized, single-blinded, sham-controlled crossover trial, 13 adults with ASD completed iTBS for 5 consecutive days over the bilateral pSTS and inion (as a sham control) in a 16-weeks interval and in a randomly assigned order. The neuropsychological function was measured with the Wisconsin Card Sorting Test (WCST) for cognitive flexibility while the clinical outcomes were measured with both self-rate and parents-rate Autism Spectrum Quotient (AQ) before and after 5-day iTBS interventions.

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Results: The results revealed significantly immediate effects of multi-session iTBS over the bilateral pSTS on parent-rate autistic symptoms in adults with ASD. The post-hoc analysis revealed the impacts of multi-session iTBS on cognitive flexibility were affected by baseline social-communicative impairment and baseline cognitive performance. Besides, the impacts of multi-session iTBS on clinical symptoms was affected by the concurrent psychotropic medication use and baseline autistic symptoms.
Conclusions: Given the caveat of the small sample size and discrepancy of multiple informants, this pilot study suggests the therapeutic potential of 5-day multi-session iTBS over the pSTS in adults with ASD. Individual factors modulating the response to rTMS should be explicitly considered in the future trial.

At a glance commentary

Scientific background on the subject

Previous studies found the importance of posterior superior temporal sulcus (pSTS) in social perception and demonstrated atypical neural mechanism of pSTS in autism. Therefore, pSTS is a potential therapeutic target of brain stimulation in autism. However, therapeutic impacts of theta burst stimulation (TBS) on pSTS in autism remain unclear.

What this study adds to the field

Our study is the first to demonstrate the feasibility and therapeutic potential applying 5-day multi-session intermittent TBS over bilateral pSTS in adults with autism. Moreover, we found therapeutic effects of TBS were modified by several baseline characteristics, which was very important in developing precision medicine in the future.

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with early-onset social communication and reprocity impairment, and repetitive, restrictive behaviors and interests [1]. Despite its disabling features, only very few interventions have shown well-validated efficacy to improve clinical outcomes in individuals with ASD. The efficacy of psychosocial interventions for adults with ASD is open to question [2]. Pharmacologically, risperidone and aripiprazole only demonstrate the effects in reducing associated symptoms, such as irritability and hyperactivity but did not alleviate core deficits in ASD [3]. Although it is suggested that oxytocin [4] and GABA modulation agents [5] are potential therapeutic options for ASD, the empirical results have been inconsistent so far. Taken together, the evidence of biological interventions for ASD is still limited. Developing novel therapeutic options, like brain stimulation, for individuals with ASD is thus pressingly needed.

Transcranial magnetic stimulation (TMS) is a noninvasive technique for brain modulation. Repetitive TMS (rTMS) can alter synaptic plasticity and long-term potentiation/long-term depression to produce long-lasting neural effects [6]. The neuromodulation effects of rTMS are translated into therapeutic benefits in several neurological and psychiatric disorders [7]. One recent consensus statement indicates the therapeutic potential of rTMS in ASD [8]. Three cortical regions are proposed in this consensus statement: the inferior frontal gyrus (social impairment and communicative deficits), the temporoparietal junction/posterior superior temporal sulcus (theory of mind, social comprehension, and attention) and the dorsolateral prefrontal cortex (comorbid depressive disorder and executive functions).

Among these target sites, prior studies have demonstrated that low-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) might improve the repetitive behaviors and modulate the executive functions in children, adolescents, and adults with ASD, whereas the therepeutic effects over social deficits are inconclusive [9–12]. Enticott and colleagues [13,14] reported that deeper rTMS delivered by H-coil at 5Hz over bilateral dorsomedial prefrontal cortex might yield a reduction of social impairment in ASD. In addition to the DLPFC and dorsomedial prefrontal cortex, the posterior superior temporal sulcus (pSTS) is another potential stimulation target for ASD [8]. Earlier studies demonstrated that the pSTS is important in the process of biological motion [15] and social perception [16]. Following studies found ASD have atypical activations of the pSTS in the social experiments [17]. One previous study found that inhibitory rTMS over the pSTS is capable of impairing the perception of biological motion, gaze perception and behaviors of orienting toward the eyes in healthy adults [18]. Moreover, our pilot study demonstrated that single-session intermittent theta burst stimulation (iTBS, a excitatory protocol) over the pSTS improves the compulsive behaviors in adults with ASD [19]. Whether the effect of single-session stimulation could be extended and expanded by different valid protocols, e.g., longer treatment duration, warrants further investigation.

Theta burst stimulation (TBS) gives bursts of three TMS pulses at a frequency of 50 Hz every 200 ms [20]. Besides, the bursts of TBS can be delivered continuously (cTBS) or intermittently (iTBS) to produce inhibitory long-term depression-like or excitatory long-term potentiation-like effects, respectively [20]. In comparison to traditional rTMS, TBS can produce similar after-effects but with shorter stimulation duration, less total TMS pulses and lower stimulus intensity [20]. These advantages may enhance the feasibility of applying TBS on challenging populations, such as autistic individuals.

Our current single-blinded, randomized, crossover and sham-controlled pilot study aimed to investigate the effects of 5-day multiple sessions of iTBS over the bilateral pSTS in adults with ASD. The clinical outcomes were measured with the

Autism Spectrum Quotient (AQ) [21] reported by both participants themselves (AQ-self) and their parents (AQ-parents), respectively. The neuropsychological outcome was measured with the Wisconsin Card Sorting Test (WCST) to assess the cognitive flexibility [22]. We hypothesized that multi-session iTBS over the bilateral pSTS would improve the social deficits and neuropsychological functions in adults with ASD.

Material and methods

Participants

We recruited participants through advertisements at the outpatient clinic of the Department of Psychiatry, Chang Gung Memorial Hospital, Taoyuan, Taiwan. Adults (older than age 18 years) with an autistic disorder, Asperger's disorder or pervasive developmental disorder, not otherwise specified according to the DSM-IV diagnostic criteria [23], were first diagnosed and assessed by a board-certificated child psychiatrist (the first author). Then, several steps were arranged once they and their families participated in our study. First, the aims and procedures of this study were described and explained in details. Second, the clinical diagnosis of ASD was further confirmed by the Chinese version of the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) [24,25]. Third, we evaluated their systemic medical disease and comorbid psychiatric disorders through clinical interviews by the child psychiatrist. Participants with a history of seizures, serious head injury, pregnancy, the presence of metal in the cranium and implanted medical device, schizophrenia, bipolar affective disorder, suicidal attempts and substance abuse were excluded from the study.

Study design

Following our previous pilot single-session trial [19], this study was a randomized, single-blinded, sham-controlled, cross-over trial to investigate the impacts of multi-session iTBS on the bilateral pSTS in intellectually able adults with ASD. All of the 19 participants who completed the single-session trial [19] were invited to enter the present multi-session trial. Thirteen of the participants were further enrolled in the randomization schedule. Among them, 6 participants were randomized to the 'pSTS then sham' group and 7 participants to the 'sham then pSTS' group. One participant did not complete this study due to personal reason (class attendance) and 12 (92.3 %) completed the entire study (Fig. 1).

In Phase 1, participants were randomly assigned to the pSTS or sham-control groups. In the pSTS group, participants received iTBS for 5 consecutive days over the bilateral pSTS. In the sham group, participants received iTBS over the inion for 5 consecutive days. The behavioral outcomes were assessed at baseline (Visit 1), post-1 day (Visit 2, one day after the last iTBS session. The same principle is applied to the expression

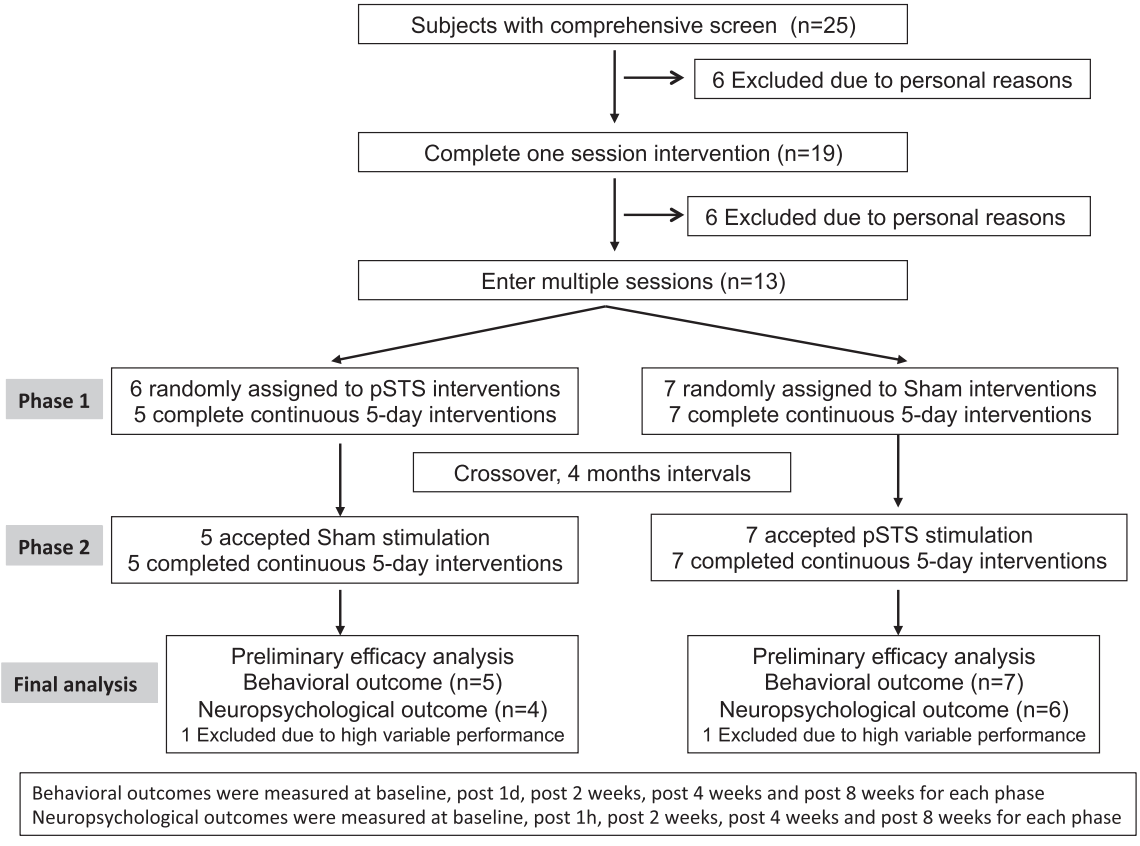

Fig. 1 Flow diagram of the randomization procedure.

""post-" henceforth), post-2 weeks (Visit 3), post-4 weeks (Visit 4) and post-8 weeks (Visit 5). The neuropsychological outcome was assessed at baseline (Visit 1), post-1 hour (Visit 2, within 1 h after the last TBS session), post-2 weeks (Visit 3), post-4 weeks (Visit 4) and post-8 weeks (Visit 5). In phase 2 (16 weeks later after the last stimulation in Phase 1 and serving as a washout period to address carry-over effect), the subjects in pSTS group in Phase 1 were shifted to the sham group and those in the sham group in Phase 1 were in the pSTS group to have 5-day sham or pSTS stimulation, respectively. In Phase 2, the behavioral outcomes were assessed before (Visit 6), post-1 day (Visit 7), post-2 weeks (Visit 8), post-4 weeks (Visit 9) and post-8 weeks (Visit 10) after the second 5-day intervention while the neuropsychological outcome was assessed before (Visit 6), post-1 hour (Visit 7), post-2 weeks (Visit 8), post-4 weeks (Visit 9) and post-8 weeks (Visit 10) after the second intervention. The results at Visit 2 stand for the immediate effect of iTBS while the results at Visits 3–5 represent the sustained effect of iTBS. The results at all time points denote the overall effect of iTBS.

Earlier studies demonstrated better after-effects within 1 h after rTMS/TBS [26–28]. We therefore arranged the psychological tests within 1 h after TBS. However, it takes time for patients and their family to observe the behavioral change in their daily life and cannot be assessed right after treatment. Behavioral outcomes were assessed one day after last intervention (post-1 day) to capture the possible effect of iTBS.

The order of randomization of the pSTS and sham stimulation followed the rules of 2 × 2 crossover design. To decrease the possible bias effect, the participants and their parents were not informed the order of stimulation. Besides, their parents were not present during iTBS interventions. This study was approved by the Research Ethics Committee at the Chang Gung Memorial Hospital (No. 99–3826B) and registered at ClinicalTiail.gov (NCT01918787) before its implementations. After the explanation of the study procedure, written informed consents were obtained from both the participants and their parents.

Stimulation target identification

T1-weighted images were collected with a 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence on a 3T MRI scanner (Trio, Siemens Medical Solutions, Erlangen, Germany), using a 12-channel head coil (TR = 2250 ms, TE = 2.6 ms, TI = 900 ms, FOV = 240 mm, Flip Angle = 9°,matrix = 240 × 256, voxel size = 1.0 × 1.0 × 1.0 mm). To ensure that the stimulated site is implicated in social processing, the location of pSTS was defined by the normalized coordinates based on the meta-analysis by Van Overwalle and Baetens [29]. This normalized region was then matched to each individual's native brain space: The original Talairach atlas coordinates of pSTS (±50, −55, 10) were first converted to the Montreal Neurological Institute (MNI) coordinates of the pSTS (±50.5, −57.1, 7.9) for registration on MR images (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The output coordinates were then marked on the native structural image in the Navigated Brain Stimulation (NBS) system (Nexstim®, Helsinki, Finland). The process of location transformation and other details have been reported elsewhere [19].

Transcranial magnetic stimulation

Surface electromyography was recorded from the right first dorsal interosseous muscle (FDI). A 70 mm figure-of-eight coil connected to a Magstim Super Rapid^2 system (Magstim Company, Oxford, UK) was used to perform TBS, and single-pulse TMS for motor evoked potentials (MEPs). The coil was placed tangentially to the scalp over the contralateral motor cortex with the handle pointing backward. The location of motor "hot-spot" was determined where TMS produced the largest MEP from the FDI at rest. We measured the active motor threshold (AMT) as the minimum stimulation intensity needed to elicit MEPs of no less than 200 μV in 5 out of 10 trials during 20 % of maximum voluntary contraction of the FDI.

Theta burst stimulation

Intermittent TBS (iTBS) protocol was applied in the current study [20]. Each TBS train was comprised of a burst of 3 pulses at 50 Hz given 1 every 200 ms for 10 times. The TBS train was given every 10 s for 20 times to have 600 pulses in total for each iTBS course. In this study, two iTBS courses, which were separated by a 5-min break, were first applied to the left pSTS and then the right pSTS in the pSTS session. As for the sham control, two iTBS courses with a break of 5 min were given to the inion. The stimulus intensity of iTBS over the pSTS was 80 % of AMT of the right FDI, while that over the inion (sham control) was 60 % of AMT with the coil flipped over [30].

Clinical symptoms outcome measurement

We used the Chinese versions of the AQ [21] questionnaires reported by participants themselves (AQ-self) and their parents (AQ-parents) separately to measure the impacts of iTBS on clinical outcomes [31]. The AQ is a 50-item questionnaire describing the clinical manifestation of ASD [31]. Every item is scored "1 (definitely agree or slightly agree)" or "0 (definitely disagree or slightly disagree)." Higher total AQ scores stand for more social deficits in ASD. Previous studies have demonstrated good psychometric properties of the AQ in adults across different cultures [32,33]. The psychometric study of the Chinese version of the AQ revealed excellent test-retest reliability (intra-class correlations: 0.65) and internal consistency (Cronbach's alpha: 0.84) [21]. The Chinese AQ has been widely used in adult ASD studies in Taiwan [34–36].

Neuropsychological function measurement

The computerized version of the Wisconsin Card Sorting Test (WCST: CV4) [37] was used to estimate mental flexibility. The participants had to choose one correct card from four categories of cards, in which the stimuli are multidimensional according to color, shape, and number and each dimension is defined by a sorting rule. By trial and error, the participant had to find the sorting rule by the feedback ("Correct" or "Wrong") that was given on the screen following each sort. After sequences of ten consecutive correct matches, the classification principle changed with no cue. The test would continue until all 128 cards were sorted, no matter if all rule shift were completed or not. The total errors in WCST were measured in

our study. Fewer total errors in WCST stand for better mental flexibility [22].

Since it is suggested that the attention capacity is associated with the performance in the WCST [38], we also used the Conners' Continuous Performance Test (CCPT) to explore and address this relationship [39]. The omission errors in the CCPT were used to test its impact in the analysis of the total errors in the WCST.

Statistical analysis

Statistical analysis was performed using the R 3.5.2 software (**R** Project for Statistical Computing, Vienna, Austria). In statistical testing, two-sided p-value ≤ 0.05 was considered statistically significant. A Wilcoxon rank-sum for continuous variables and a chi-square test for categorical variables were conducted to examine whether the individual characteristics at baseline differed between 'pSTS then sham' group and 'sham then pSTS' groups. Within group comparisons were conducted to examine the differences of WSCT total errors, AQ-self scores, and AQ-parents scores. Within groups comparisons using Wilcoxon signed-rank were conducted in each group with baseline (Visit 1) as the reference for Visit 2 to Visit 5, as well as Visit 6 as the reference for Visit 7 to Visit 10.

To examine the crossover change of pSTS vs. sham stimulation in the 2 stimulation Phase, because one participant did not receive intervention, we used the modified intention-to-treat analysis with post-randomizaiton deletion to examine the group effect. This modified intention-to-treat analysis has demonstrated a capacity of not biasing the trial results [40]. Furthermore, we conducted an analysis to those with very high variable performance in the WCST as our sensitivity analysis. The *generalized estimating equations* (GEE) was used to account for the correlations between the repeated measurements with an AR (1) correlation structure based on the CONSORT 2010 statement: extension to randomised crossover trials [41]. To address possible bias of carryover effect in our randomized crossover study design, we used a 16-week washout period between the pSTS and sham stimulation, and the carryover effect was expected to vanish and to be minimal after the washout period.

To detect possible factors related to the crossover group of pSTS vs. sham stimulation throughout overall stimulation periods and immediate response after 5-day multi-session iTBS, we used the GEE model with change score of pSTS vs. sham stimulation as the outcome variable and individual characteristics at baseline as the predictors in overall stimulation periods, and stratified by stimulation periods.

Results

Demographic data

The baseline demographic data of participants are described in Table 1. Overall, there were similar distributions of baseline demographic data and behavioral symptoms for these two randomized groups (all $p > 0.05$).

The participants maintained the same medications throughout the whole study period. Specifically, two participants took psychotropic medications (one took 40 mg fluoxetine per day, the other took 30 mg sertraline, 20 mg methylphenidate and 0.5 mg alprazolam per day).

Table 1 Demographic and baseline data by all participants and by randomization schedule, N = 13.

Demographic characteristics	Total	Randomization schedule		
		pSTS then sham	sham then pSTS	p value
N	13	6	7	
Age, mean (SD)	22.7 (1.4)	23.2 (1.5)	22.4 (1.4)	0.473
Gender, male (%)	11 (84.6 %)	5 (83.3 %)	6 (85.7 %)	1.000
Education level (n)				
Senior high school or lower	3	1	2	1.000
College	10	5	5	
Full-scale IQ, mean (SD)	102.9 (17.4)	110.3 (18.8)	96.6 (14.6)	0.165
Verbal IQ, mean (SD)	98.8 (21.1)	106.2 (23.5)	92.4 (18.0)	0.258
Performance IQ, mean (SD)	106.0 (16.2)	111.3 (17.3)	101.4 (15.0)	0.291
ADOS				
Reciprocal social interaction (3~12), mean (SD)	6.3 (2.7)	6.0 (3.5)	6.9 (2.1)	0.722
Language and communication (2~7), mean (SD)	3.8 (1.8)	3.8 (1.9)	4.0 (1.9)	0.980
Stereotyped behaviors and restricted interests (1~2), mean (SD)	1.2 (0.6)	1.2 (0.4)	1.2 (0.7)	0.918
Total AQ-parents, mean (SD)	27.6 (7.9)	23.8 (8.9)	32.9 (6.0)	0.110
Total AQ-self, mean (SD)	32.4 (7.3)	31.8 (9.1)	30.9 (5.5)	0.812
Medications (n)				
Sertraline (30 mg/day)	1	0	1	–
Fluoxetine (40 mg/day)	1	0	1	–
Methylphenidate (20 mg/day)	1	0	1	–
Alprazolam (0.5 mg/day)	1	0	1	–

Abbreviations: pSTS: posterior superior temporal sulcus; IQ: intelligence quotient; ADOS: Autism Diagnostic Observation Schedule; AQ: Autism Spectrum Quotient

Table 2 Neuropsychological and behavioral outcomes before and after interventions.

	Phase 1									Phase 2								
	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	Visit 7		Visit 8		Visit 9		Visit 10	
	Baseline	Post 1 h/d		Post 2w		Post 4w		Post 8w		Baseline	Post 1 h/d		Post 2w		Post 4w		Post 8w	
	mean (SD)	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value	mean (SD)	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value	mean (SD)	Wilcoxon *p* value
pSTS then sham																		
WCST Total errors	5.6 (2.6)	10.4 (8.9)	0.11	9.2 (6.0)	0.14	8.2 (3.6)	0.08	8.8 (3.7)	0.10	7.6 (2.3)	4.8 (3.1)	0.66	6.6 (7.1)	0.69	5.6 (4.5)	0.29	5.2 (4.0)	0.34
AQ-self	26.0 (8.0)	30.2 (9.7)	0.10	25.6 (11.5)	0.72	26.2 (10.5)	0.89	27.8 (11.8)	0.50	27.0 (10.5)	26.0 (9.9)	0.20	26.6 (11.2)	0.72	25.0 (11.8)	0.10	25.4 (11.8)	0.27
AQ-parents	30.4 (9.3)	27.4 (9.8)	0.07	27.8 (9.3)	0.07	29.2 (11.2)	0.58	29.0 (10.1)	0.46	31.2 (7.5)	31.6 (9.6)	0.58	28.8 (10.1)	0.14	27.8 (10.1)	0.07	30.6 (9.8)	0.59
sham then pSTS																		
WCST Total errors	12.6 (9.4)	11.7 (7.1)	0.75	10.4 (7.7)	0.18	11.0 (7.3)	0.17	12.9 (13.8)	0.83	9.0 (6.1)	9.3 (6.3)	0.91	13.0 (12.8)	0.18	11.6 (13.1)	0.61	10.6 (11.3)	0.75
AQ-self	30.9 (5.5)	30.6 (5.1)	0.60	29.0 (4.0)	0.20	29.7 (3.8)	0.32	27.9 (4.1)	0.03	27.7 (5.4)	28.3 (3.6)	0.15	27.7 (5.9)	0.92	29.0 (4.1)	0.40	30.3 (4.6)	0.75
AQ-parents	32.9 (6.0)	34.6 (6.9)	0.92	31.9 (8.7)	0.87	33.1 (6.8)	0.67	32.6 (9.8)	0.15	33.1 (7.7)	32.9 (11.7)	0.92	33.3 (8.2)	0.89	34.6 (8.5)	0.23	33.9 (7.2)	0.69

Abbreviations: pSTS: posterior superior temporal sulcus; WCST: Wisconsin Card Sorting Test; AQ: Autism Spectrum Quotient; d: day; h: hour; w: week.
Within-treatment-group using Wilcoxon signed-rank, as referenced to Visit 1 for other Visits in Phase 1; referenced to Visit 6 for other Visits in Phase 2. Only uncorrected *p* values were presented. With Bonferroni's method to correct for multiple comparisons, p value < 0.0125 is considered significant.

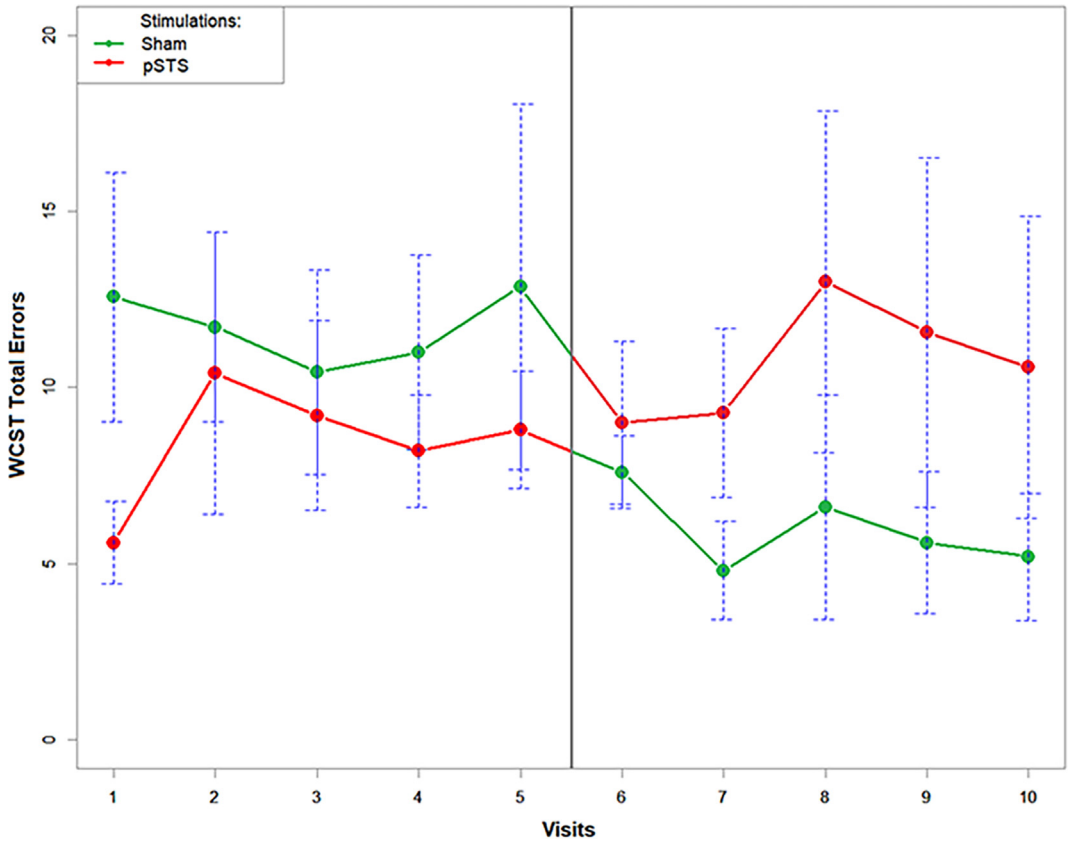

Fig. 2 Group mean plot with standard error on the total errors of the Wisconsin Card Sorting Test (WCST) by time and condition. The solid lines mean group mean while the dash lines mean standard errors.

The raw data of neurological and behavioral outcomes

The neurological and behavioral outcomes of 'pSTS then sham' group and 'sham then pSTS' group of 10 visits were listed in Table 2 and Figs. 2–4. Because 2 participants showed high variable performance in the WCST (ID = 4036C11 and 4036C24, Supplementary Figure 1), their data were excluded in the sensitivity analysis of the WCST.

As shown in Figs. 2–4, no significant changes of the neuropsychological and behavioral outcomes in comparison to baseline (Visit 1 in Phase 1 and Visit 6 in Phase 2) for both 'pSTS than sham' and 'sham then pSTS' group in Phase 1 and Phase 2, which reflecting the results of not statistical significance in Table 2. Although there was a decrease immediately after 5-day iTBS in AQ-parents total score [Fig. 4], this was not statistically significant [Table 2], and was not observed in the WCST total score [Fig. 2] and total scores of AQ-self [Fig. 3].

The crossover group effect between pSTS vs. sham intervention

As shown in Table 3, we found a significant immediate group effect of multi-session iTBS ($p = 0.042$): Participants had lower total scores of AQ-parents under pSTS vs. sham intervention 1 day after 5 consecutive iTBS sessions. However, we found partitipants had higher total scores of AQ-self under pSTS vs. sham intervention 8 weeks after the intervention ($p = 0.001$).

As for the sustained and overall group effect of multi-session iTBS in the total errors of WCST, we did not find any significant results. In the sensitivity analysis, we did not find immediate, or sustained and overall group effect of multi-session iTBS on the total errors of WCST, neither (Supplementary Table 1).

The factors related to the crossover group effect

Table 4 shows that baseline communication ($p = 0.043$) and social ($p = 0.011$) impairment on the ADOS were related to immediate group effect on the total errors of WCST. Participants with more severe baseline communication and social impairment had higher total errors of WCST in the pSTS vs. sham intervention 1 h after multi-session iTBS. In addition, we found that the omission errors of CPT at baseline were related to the overall group effect on the total errors of WCST ($p = 0.001$). Participants with higher omission errors of CPT at baseline had lower total errors of WCST in pSTS vs. sham intervention in the overall study periods after multi-session iTBS. In the sensitivity analysis (Supplementary Table 2), the impacts of baseline CPT omission errors on overall WCST total errors remain similar ($p = 0.017$). Moreover, we found higher FIQ at baseline was related to higher total errors of WCST in pSTS vs. sham intervention in the overall study period after multi-session iTBS ($p = 0.041$).

Baseline communication ($p = 0.029$) and social ($p = 0.039$) impairment on the ADOS was related to the overall group

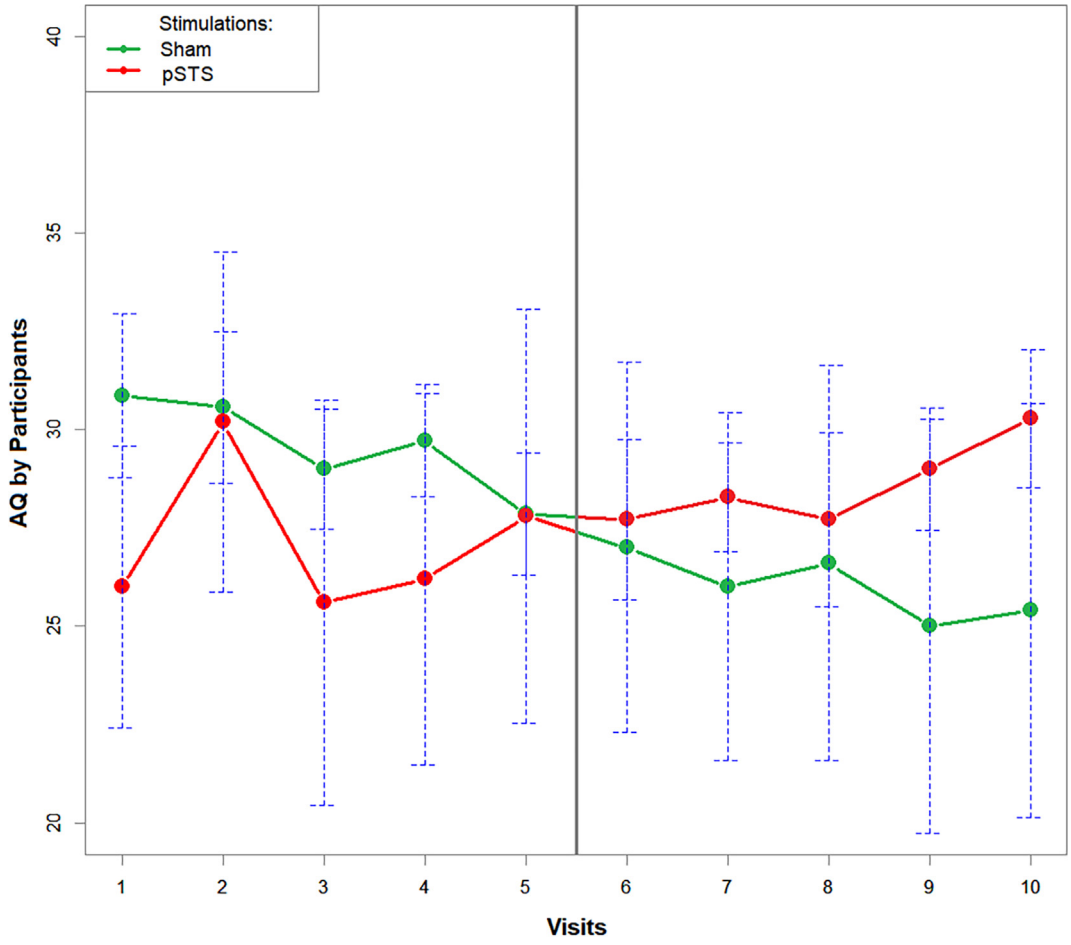

Fig. 3 Group mean plot with standard error on the total scores of the self-report Autism Spectrum Quotient (AQ) by time and condition.
The solid lines mean group mean while the dash lines mean standard errors.

effect on the total scores of AQ-self. Participants with higher baseline severity of language and social function had higher total scores of AQ-self in the active vs. sham intervention in the overall study period after multi-session iTBS.

Baseline total scores of AQ-parents were related to immediate group effect on total scores of AQ-parents ($p = 0.013$). Participants with higher baseline AQ-parents total scores had higher total scores of AQ in the active vs. sham intervention post 1d after continuous 5 day iTBS intervention. Moreover, we found baseline social impairment on the ADOS was related to the overall group effect on total scores of AQ-parents ($p = 0.038$). Participants with higher baseline severity of social sumptoms had lower AQ-parents total scores in the active vs. sham intervention in the overall study period after multi-session iTBS. Moreover, participants with concurrent medication use had higher AQ-parents total scores in the active vs. sham intervention in the overall study period after multi-session iTBS ($p = 0.031$).

Discussion

In this randomized, single-blinded, sham-controlled and crossover study, we found that there existed the therapeutic potential of 5-day multi-session iTBS over the bilateral pSTS on clinical sympotms but not executive function (i.e. cognitive flexibility) in intellectually able adults with ASD. Our post-hoc analysis identified that baseline social-communication symptoms, concurrent psychotropic medication use and IQ might modulate the effects of iTBS on the clinical symptoms and cognitive flexibility in adults with ASD. Notably, all of these results should be interpreted conservatively because of the small sample size in this pilot study.

Corresponding to the theoretical speculation [8] and our previous one-session trial [19], our study demonstrated the therapeutic potential of 5-day multi-session iTBS on the pSTS in adults with ASD, in terms of improvement in parent-rated autistic symptoms one day immediately after the intervention. However, these results were not compatible to our recent randomized sham-controlled single-blind trial in children and adolescents with ASD (N = 78) [42], which suggests that iTBS on the bilateral pSTS twice per week for continuous 4 weeks did not significantly have any effects on autistic symptoms and social cognitive performance in autistic youth. The inconsistent results might be explained by several reasons. First, the small sample size in the current pilot study did not have enough power to unveil significant effects of the intervention. The second possible explanation is that the optimal rTMS protocol for people with ASD, especially the total

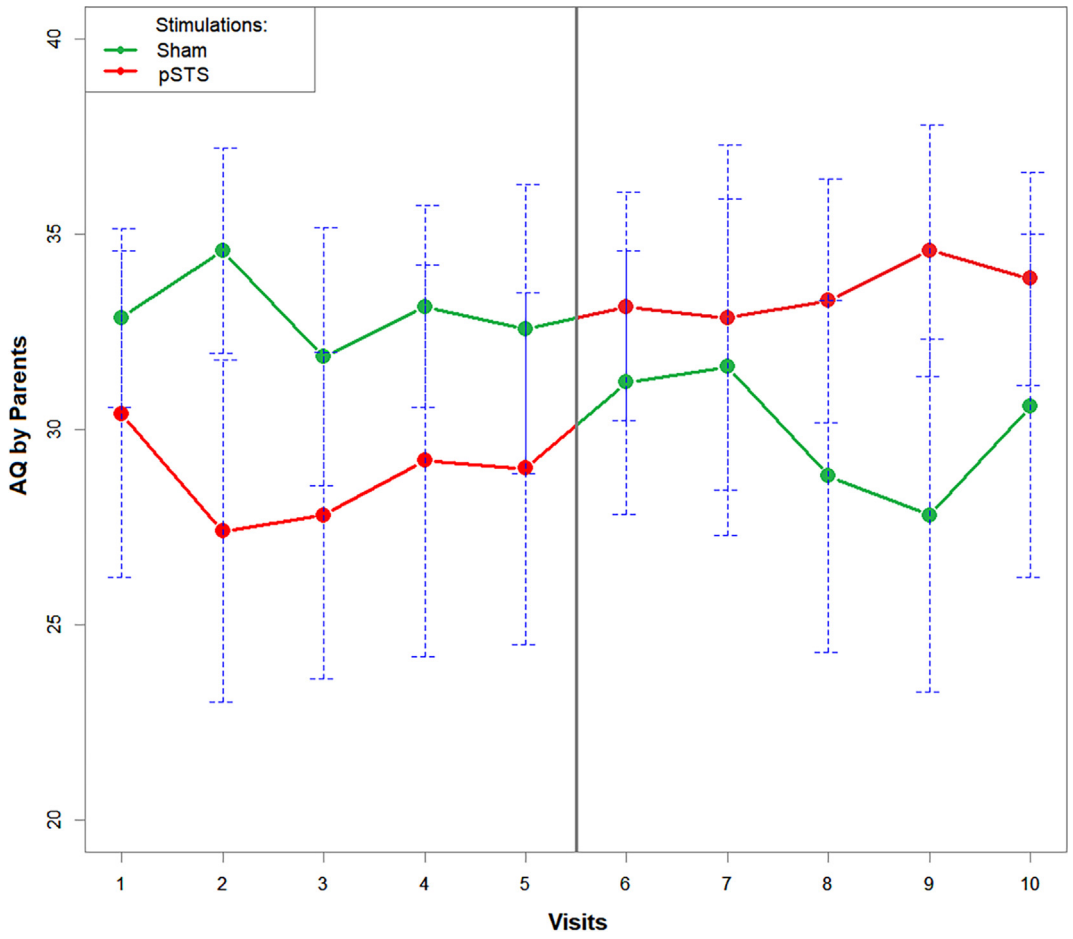

Fig. 4 Group mean plot with standard error on the total scores of the parents-report Autism Spectrum Quotient (AQ) by time and condition.
The solid lines mean group mean while the dash lines mean standard errors.

sessions per week, has still been elusive. Earlier rTMS studies applied 1-to-2-session intervention per week [9,11,12], but recent rTMS studies applied 5-session intervention per week in ASD [43]. The current study suggests that more rTMS/TBS sessions per week might have better therapeutic impacts on people with ASD, consistent with the standard protocol applied to people with major depressive disorder [44].

Our results demonstrated the potential modulation of several clinical factors on the therapeutic responses. The first factor is the baseline clinical severity. Consistent with an earlier study on major depressive disorder demonstrating the association between the baseline level of depressive symptoms and the remission rate of rTMS interventions [45], we also found the effects of iTBS over the pSTS regarding the cognitive flexibility and autistic symptoms were also affected by the baseline clinical severity. The participants with higher baseline severity of social-communicative impairment had less benefits in the immediate effect of iTBS on the total errors of WCST and in the overall effect of iTBS on self-report autistic symptoms. Interestingly, we found that the participants with higher baseline severity of social impairment improved more in parents-report autistic symptoms from the overall effect of iTBS. Similarly, we identified improvement in parent-report autistic symptoms one immediately after the iTBS, but deterioration in self-report

Table 3 Crossoveer group effect between pSTS vs Sham intervention.

	WCST Total errors		AQ-self		AQ-parents	
	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value	Estimate (SE)	*p* Value
Overall group effect	−0.18 (1.83)	0.923	1.03 (0.73)	0.162	−0.93 (0.98)	0.343
Group effect at Post 1 h/1d	0.92 (2.21)	0.679	0.42 (1.60)	0.795	−2.75 (1.35)	0.042
Group effect at Post 2w	2.58 (1.43)	0.070	−1.17 (1.33)	0.379	0.42 (0.88)	0.635
Group effect at Post 4w	1.42 (1.40)	0.310	0.08 (0.79)	0.917	1.42 (0.74)	0.056
Group effect at Post 8w	0.17 (1.38)	0.904	2.42 (0.70)	0.001	0.08 (1.26)	0.947

Abbreviations: WCST: Wisconsin Card Sorting Test; AQ: Autism Spectrum Quotient; d: day; h: hour; w: week.

Table 4 Factors related to crossover group effect.

	Post 1 h/1d		Overall	
	Estimate (SE)	*p*-value	Estimate (SE)	*p*-value
WCST Total errors				
Age	1.33 (1.66)	0.443	0.24 (0.57)	0.674
FIQ	−0.14 (0.13)	0.315	−0.09 (0.08)	0.238
Gender	1.70 (6.48)	0.798	1.83 (1.68)	0.278
Baseline WCST	−0.21 (0.31)	0.517	−0.02 (0.10)	0.806
Baseline severity of language in ADOS	2.92 (1.26)	0.043	1.22 (1.09)	0.261
Baseine severity of social in ADOS	2.42 (0.78)	0.011	1.17 (0.66)	0.075
Baseline severity of RRB in ADOS	−1.49 (4.35)	0.740	−1.78 (0.96)	0.063
Medication	−4.70 (6.33)	0.475	−2.55 (1.49)	0.087
CPT omission errors at Post 1 h/1d	−0.71 (0.37)	0.087		
CPT omission errors at Baseline			−0.10 (0.02)	0.001
AQ-self				
Age	0.97 (1.20)	0.437	0.59 (0.39)	0.128
FIQ	0.01 (0.10)	0.934	0.01 (0.05)	0.993
Gender	−0.10 (4.72)	0.984	−0.99 (1.64)	0.546
Baseline AQ	−0.35 (0.25)	0.183	−0.13 (0.12)	0.259
Baseline severity of language in ADOS	0.06 (1.13)	0.956	0.87 (0.40)	0.029
Baseine severity of social in ADOS	0.61 (0.77)	0.451	0.59 (0.29)	0.039
Baseline severity of RRB in ADOS	−5.05 (2.74)	0.095	−0.31 (1.15)	0.787
Medication	−7.10 (4.15)	0.118	−1.43 (0.89)	0.107
AQ-parents				
Age	−0.68 (1.02)	0.520	−0.23 (0.38)	0.537
FIQ	0.02 (0.09)	0.851	−0.01 (0.06)	0.978
Gender	2.70 (3.87)	0.502	−1.54 (1.25)	0.220
Baseline AQ	0.46 (0.15)	0.013	0.18 (0.13)	0.164
Baseline severity of language in ADOS	0.05 (0.95)	0.957	−0.40 (0.26)	0.123
Baseine severity of social in ADOS	−0.37 (0.66)	0.591	−0.37 (0.18)	0.038
Baseline severity of RRB in ADOS	1.40 (2.63)	0.607	−0.62 (1.77)	0.725
Medication	0.30 (3.97)	0.941	2.17 (1.01)	0.031

Abbreviations: WCST: Wisconsin Card Sorting Test; AQ: Autism Spectrum Quotient; FIQ: Full intelligence quotient; ADOS: Autism diagnostic observation schedule; RRB: Restricted and repetitive behaviors; d: day; h: hour; w: week

symptoms 8 weeks after the intervention. The wisdom from the brain stimulation studies on major depressive disorder does not indicate such a long carry over effect or such a delayed onset of therapeutic response from the rTMS [46]. This inconsistency may thus in part arise from report bias between multiple informants [47,48], especially in intellectually able people with ASD [49]. Suboptimal test-retest reliability of self-report AQ administered in adults with ASD [50] may also play some role, especially that the participants had completed the full form of AQ for 10 times (8 weeks after the interventions was the Visit 10) in the present unique design. Extending the previous advise [51], the current findings suggest the importance of involving multiple informants when assessing autistic traits in clinical trials. Moreover, these unresolved results also raise an open question about the stability and consistency of self-rate questionnaires on autistic traits over time [50], as well as what the assessment frequency would be to have better test-rest reliability.

The second factor which might modulate participants' response to intervention is the individual's intelligence. Our results revealed those with higher FIQ and better attention had more total errors of WCST in the pSTS vs. sham interventions. However, our recent study in youth with ASD revealed participants with higher FIQ might have higher improvements in the Frith-Happe Animation Task (a social cognitive task involving mentalization) [42]. The inconsistency might come from different study protocols, sample sizes and neuropsychological measurements. The impacts of baseline cognitive performance on therapeutic effects of iTBS on neuropsychological functioning in ASD deserved further investigations. The third factor is the concurrent medication use. Previous studies with single or paired-pulse paradigms of TMS demonstrated effects of psychotropic medications on cortical excitability and inhibition [52]. The concurrent use of benzodiazepine and/or psychostimulant may influence rTMS treatment outcomes in people with major depressive disorder [53]. We found that participants with concurrent psychotropic medication use benefited less from the iTBS in the total scores of AQ-parents. The impacts of concurrent mediation use during brain stimulation in ASD, regardless of the benefits or disadvantages, should be specifically examined in the future study.

The present findings need to be interpreted conservatively in light of the aforementioned limitations and the following caveats. First, although the WCST is a common neuropsychological measurement in clinical settings for ASD, the cognitive constructs, such as cognitive flexibility, strategic planning, working memory, etc, which this task assesses do not directly implicate the function of pSTS. Moreover, learning effects on the cognitive performance might exist because the WCST was repeatedly conducted within 5 days. In the future, more neuropsychological pertinent assessments, more objective outcome measures (e.g., functional neuroimages), other sensitive clinical measurements and analytical strategies (e.g., qualitative approaches), larger sample sizes, different intervention protocols and longer therapeutic sessions are required to explore the therapeutic effects of iTBS over the pSTS and the moderators of the effects in individuals with ASD. Second, as a follow-up of the previous pilot study, only 12 out of 19 participants who were enrolled in earlier the single-session trial [19] completed the current trial. Therefore, the limited sample size may not have adequate statistical power to discover all potential effect. Third, a generic limitation in the randomized crossover trials is the carry-over effect. Senn [54] suggested using a long washout period, rather than adjusting it in the statistical model, to eliminate the possible carry-over. In the current study, we used a 16-week washout period to eliminate the possible carry-over between pSTS and sham interventions. Given the long washout period, we should expect no or only a minimal carry-over effect.

Conclusions

In sum, given the small sample size and discrepancy in self- and parents-rate autistic traits, we found potential therapeutic

effects of multi-session (for 5 consecutive days) iTBS over the pSTSs on parents-rate clinical symptoms in intellectually able adults with ASD. We also identified several factors, which might modulate the therapeutic effects of iTBS over the pSTS on ASD. If the current identified factors could be replicated in a larger sample with chronically administered rTMS stimulations, these factors may facilitate the better development of therapeutic strategies and the selection of responders for non-invasive brain stimulation treatment for ASD.

Conflicts of interest

The authors have no financial or ethical conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhydene.2021.07.028.

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