The Impacts of Theta-burst Stimulation Over Posterior Superior Temporal Sulcus on Children and Adolescents With Autism Spectrum Disorder

ID: NCT03621189

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【2020/12/14】

Design

This was a 4-week randomized, parallel, single-blind and sham-controlled trial, followed by another 4-week open-label intervention, to investigate the feasibility and efficacy of iTBS over the bilateral pSTS in children and adolescents with ASD at Chang Gung Memorial Hospital (CGMH, Linkou, Taiwan). There were 2 phases in this RCT, with one-month follow-up. Specifically, after baseline assessments, participants were randomized to the Active or Sham group (Phase 1, Baseline-Week 4). Given limited human resources, the investigator (H.-C.N.) and his assistant assessed and delivered rTMS to all participants. Therefore, only participants and their caregivers were blind to the treatment condition (single-blind). Active versus sham iTBS was administered over the pSTS 2 days/week for 4 weeks. Entering Phase 2 (Week 5-8), participants were unblinded, and then active iTBS over the pSTS were administered to all participants 2 days/week for the other 4 weeks. This distinct design allowed for a conventional rigorous RCT of low risk of bias (Phase 1), and concomitantly resolved a potential inequity issue by providing access to iTBS for every participant (Phase 2) (Green, 2008). This also enabled investigating effects of longer treatment courses. Considering the feasibility based on their school activities, participants freely chose 2 intervention days, which are at least 48 hours apart from each other, from Monday to Saturday in the beginning of their interventions. Once they made the choice, the schedule of sessions was fixed throughout the trial.

Clinical assessments were completed in participants within one week of the first iTBS session of Phase 1 (Baseline) and Phase 2 (Week 5), following the last iTBS session (Week 8), as well as at follow-up (Week 12). With the same baseline and follow-up assessment schedule, social cognition was specifically measured within 1 hour following the last iTBS session of Phase 1 and 2, respectively.

A minimum total sample size of 68 was estimated using G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009), being powered (90% power and two-sided 5% significance) to detect a standardized effect at 0.4 from within-between interaction of the repeated-measure ANOVA model. The estimated effect size was guided using the pool effect on social behavior deficits in existing studies (Barahona-Correa et al., 2018).

Before implementation, this study was approved by the Research Ethics Committee at CGMH (104-9413A) and registered with ClinicalTrials.gov (NCT03621189). The procedures and purpose of the study were explained face-to-face to participants and their parents, who then provided written informed consents.

Participants

We recruited participants, aged 8-17 years, with ASD from the psychiatry outpatient clinic of CGMH, Linkou, Taiwan. DSM-IV autistic disorder or Asperger's

disorder, or DSM-5 ASD was clinically diagnosed and corroborated using the Autism Diagnosis Objective Schedule (Lord et al., 2000). Exclusion criteria included: FIQ<70 based on the Wechsler Intelligence Scale for Children-3rd or Wechsler Adult Intelligence Scale-3rd (a cutoff at 16 years), any prior history of major neurological (especially epilepsy) or medical illness, mood and anxiety disorders, schizophrenia and substance misuse. Participants with co-occurring attention-deficit hyperactivity disorder (ADHD) were included, and assessed by experienced child psychiatrist (H.-C.N., Y.-Y.W., H.-Y.L.). Since there are high psychiatric comorbidities in ASD (70% at least one comorbidity), we intended to design the current protocol to strike a balance between the generalizability, feasibility, as well as the heterogeneity resulted from the psychiatric comorbidities. Therefore, we decided to include those comorbid with ADHD, which is the most common co-occurring condition, has similar neurodevelopmental nature, and might share some etiologies with ASD, but exclude people with the co-occurring conditions which may happen in association with ASD but are not inherent in neurodevelopmental conditions (i.e., these disorders happen chronologically after ASD). Simultaneously, the effect of iTBS over the pSTS on other major psychiatric disorders are unknown, but is well tolerated in people with co-occurring ADHD (Ni et al., 2017). To minimize potential harms and heterogeneity, people with co-occurring mood and anxiety disorders, schizophrenia and substance misuse were thus excluded from the current trial. All psychotropic medications were continued without change during the trial. All participants had been naïve to any non-invasive brain stimulation treatment.

Intervention

A 70-mm figure-of-eight coil connected to a Magstim Super Rapid^2 system (Magstim Company, Oxford, UK) was used. Initially, 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 single-pulse TMS produced the largest motor evoked potentials (MEPs) 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 uV in 5 out of 10 trials during 20% of maximum voluntary contraction of the FDI.

This study administered the iTBS protocol (Huang et al., 2005) as follows: Each TBS train was comprised of a burst of 3 TMS pulses at 50 Hz, at 200 ms intervals, for 10 times. The TBS train was delivered every 10 seconds for 20 times to have 600 pulses in total for each iTBS course. In each iTBS session, we first delivered two iTBS with a 3-minute break over the left pSTS. 5 minutes later, we then delivered the other two iTBS over the right pSTS. The intervention pulses in each session were 1200 for each

hemisphere (in total 2400 pulses/session; 38400 pulses/study). The stimulus intensity of iTBS over the pSTS was 80% of AMT for the active intervention, but 60% AMT for the sham intervention. The sham stimulation was still targeted on the bilateral pSTS, but delivered with the coil tilted one-wing 90° off the head (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001), which is a valid sham condition commonly used in double- or single-blind sham-controlled RCT across major psychiatric disorders (Lefaucheur et al., 2020). This one-wing 90° tilted coil sham manipulation is devoid of detectible biological effects (Lisanby et al., 2001) and produces haptic and auditory simulation. No any participant assigned in the Sham group at Phase 1 actively disclosed or guessed that he or she received the sham stimulation.

The location of the bilateral pSTS was defined based on the meta-analysis of functional MRI (Van Overwalle & Baetens, 2009). These regions were registered to each individual's native structural image in the Navigated Brain Stimulation system (Nexstim®, Helsinki, Finland). The details of localization process are reported elsewhere (Ni et al., 2017). Whether the lateralization exist in function of the pSTS remains elusive. Unlike the target site selection in depression, one recent study demonstrated 18 sessions of rTMS applied over bilateral DLPFC produces the most striking positive effects on improving symptoms in children and adolescence with ASD (E. M. Sokhadze et al., 2018). Furthermore, our prior preliminary study also shows the potential therapeutic effects of bilateral pSTS stimulation in adults with ASD (Ni et al., 2017). We thus followed this principle to set the target site at the bilateral pSTS.

Outcomes

The primary outcomes included the safety profiles, as well as the social deficits as measured by the caregiver-rated Social Responsiveness Scale (SRS) (Gau, 2013), since theoretically targeting the pSTS is aimed to modulate the activity within the social brain network. Atypical social cognition is often associated with the autistic symptoms. The secondary outcomes thus included two common tasks assessing the social cognition performances of people with ASD (Barahona-Correa et al., 2018), i.e., the Reading the Mind in the Eyes test (RMET) (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; T. S. Li et al., 2020) and Frith-Happe Animations Task (White, Coniston, Rogers, & Frith, 2011) (Barch et al., 2013). Notably, these two tasks, nonetheless, are not specific to the pSTS activities. Given our preliminary beneficial results in compulsory behaviors in adults (Ni et al., 2017), we also adopted the Repetitive Behavior Scale-Revised (RBS-R) (Bodfish, Symons, Parker, & Lewis, 2000; Y. C. Yang et al., 2019) as the exploratory outcome. Higher scores on the SRS and RBS-R represent greater severity of the two domains of autistic symptoms. RMET total scores represent how many correct mental states the participant has inferred from the eyes, indicating

individual's theory of mind capability. Frith-Happe Animations also tap mentalizing capacity by asking the participant to infer whether interaction intents exist between two triangles. When the participant answered about the presence/absence of interactions, he/she was further asked to select words that best described how these triangles were feeling at the end of each video clip. Participants scored 1 point for correct answers to either presence/absence or exact description of mental states, which are summarized as the total Categorical scores and Feelings scores, respectively. To enhance a contrast and reduce assessment time, we adopted the revised Frith-Happe Animations following those used in the Human Connectome Project (Barch et al., 2013), which only included social and random interactions.

Side effects were assessed immediately after each session and at one-month follow-up using open-ended questions inquiring any physical discomfort and then close-ended questions including "pain at application site", "headache/dizziness", "tinnitus" and "anxiety" experienced during and after iTBS

Statistics

Herein we only reported clinical and cognitive data during RCT. Independent t-test and chi-square test were used to evaluate the difference of baseline characteristics. To simultaneously examine the immediate effect of pSTS vs. sham stimulation in different visits, the generalized estimating equations (GEE) model was conducted using the data of Baseline, Week 4, and Week 8. To account for correlations between individuals' repeated measurements between visits, a working correlation matrix with a first-order autocorrelation was used with the robust estimator of standard error. Treatment, Time, and a two-way interaction (Active vs. Sham × Time) effects were modeled in the GEE. The maximum likelihood method in the GEE was used to address the missing values from dropouts. In consideration of high inter-individual variability in the clinical symptoms and social cognitive function at baseline, we also implemented an additional analysis using the symmetrized percentage change (Ayers, 2006) to investigate the iTBS effects. Because there was significant difference for both groups at baseline in the RMET, all of the analyses in the GEE and symmetrized percentage change were adjusted.

To comprehensively examine effects across time for both conditions, exploratory within-group comparisons were also conducted in the same GEE regardless of whether the main effect was statistically significant. However, when the main effect of GEE is not statistically significant, the significant findings in these exploratory within-group comparisons should be interpreted conservatively. The correction for multiple comparisons was implemented to avoid type-I errors. Five pairwise within-group comparisons (i.e., Baseline vs. Week 4, Baseline vs. Week 8, Baseline vs. Week 12,

Week 4 vs. Week 8, Week 8 vs. Week 12) were calculated separately in Active (8-week active TBS) and Sham (4-week sham followed by 4-week active TBS) groups.

Considering clinical heterogeneity in ASD, we defined responders based on the Reliable Change Index (RCI) calculated using the SRS total scores. The RCI takes into consideration the false positive outcome that could occur due to random error from repeated measurements alone (Jacobson & Truax, 1991). The RCI represents differences in individual's scores between before- and after-intervention, divided by the standard error of the difference of the measure. Responders were those with RCI >1.64, which corresponds to $p<0.05$ with one-sided test (i.e., the null hypothesis was that iTBS would not help with social symptoms). Demographic and clinical features were compared between the responders and non-responders using non-parametric tests.

In addition to the stratified analysis based on responsiveness, we also tested a three-way interaction (Active vs. Sham × Time × Modifier) to explore whether iTBS over the pSTS is more beneficial for individuals with ASD with certain characteristics. Effect modifiers included demographics, intelligence quotient, clinical traits, comorbidity, and medication.

Statistical analysis was performed using the SAS Version 9.4 software (SAS Institute, Cary, NC, USA). Considering multiple comparisons including the clinical symptoms and social cognitive function (5 measurements), the GEE, within-group analyses and three-way interaction were considered statistically significant at *p-value*≤0.01. Despite contention, herein, alpha level in-between 0.01 and 0.05 were considered a nominal significance for hypothesis generating for the future study (Bays, 2019).

Community involvement

There were no community stakeholders involved in the development of research questions, study design and outcome measurements. Taipei Parents Association of Autism and Foundation for Autistic Children and Adults in Taiwan helped us to disseminate the recruitment notice during the study implementation, as well as provided the platform for knowledge translation and dissemination of the current findings to parent groups after the completion of the study. The progress report has been submitted to the funding agency, and the findings have been summarized in a user-friendly language and been feedbacked to the participants and their caregivers.

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