



Precise theta burst transcranial magnetic stimulation selectively reduced duration-related mismatch negativity

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ABSTRACT

Background: Mismatch negativity (MMN) is a typical event-related potential component reflecting pre-attentive processing. MMN impairment, especially reduced duration-related MMN (dMMN), has been suggested as a potential predictive biomarker for the onset of schizophrenia.

Objective: This study attempts to manipulate specific MMN activities using advanced neuroimaging-guided intermittent theta-burst stimulations (iTBS), which will be helpful to uncover the sources of MMN generation and contribute to the development of new clinical treatments.

Methods: Twenty-four healthy volunteers were recruited and participated two-session modulations consisting of active and sham iTBS. iTBS was precisely delivered over individual right posterior superior temporal cortex (pSTG). Before and after each iTBS session, two MMN components evoked by duration and frequency deviants were quantified respectively.

Results: A significant interaction of time and iTBS was observed on dMMN amplitudes, but not frequency-related MMN amplitudes. dMMN only decreased after active precise iTBS intervention, but did not after sham iTBS. The post effect of iTBS on dMMN was found in 16 of 20 subjects, suggesting a robust effect even at individual level. Furthermore, sLORETA analysis showed that the lateralization of STG activation was reversed after the active iTBS.

Conclusions: We applied a precise strategy for neuroimaging-guided iTBS modulation over the right pSTG, which is promising in selectively modulating MMN for specific deviants.

1. Introduction

Pre-attentive processing is an important ability for human beings because it allows them to detect changes in a complex environment without allocating limited attentional resources (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005). This process consists of the automatic detection of changes and the subsequent shift in attention, which can be reflected by a typical event-related potential (ERP) component, mismatch negativity (MMN) (Doeller et al., 2003; Garrido, Kilner, Stephan, & Friston, 2009). Auditory MMN can be elicited by an auditory oddball paradigm in which subjects are instructed to ignore auditory sounds.

Standard sounds repeat with high probability while deviant sounds interrupt these repetitions with rare probability (Todd, Harms Lauren, Schall Ulrich, & Michie Patricia et al., 2013). Reduced auditory MMN is related to impaired sensory-processing and cognitive deficits in psychiatric disorders (Kremláček et al., 2016). In particular, a systematic review of MMN studies in schizophrenia suggests that MMN impairment is a potential biomarker of disease risk and progression (Erickson, Ruffle, & Gold, 2016; Kircher et al., 2004; Nagai et al., 2013; Perez et al., 2014). Reduced MMN amplitudes were consistently found in both chronic and first-episode patients with schizophrenia (Umbricht & Krljes, 2005). These MMN deficits existed even before the onset of

Abbreviations: dMMN, duration-related mismatch negativity; ERP, event-related potential; fMMN, frequency-related mismatch negativity; iTBS, intermittent theta burst stimulation; MEP, motor evoked potential; MMN, mismatch negativity; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; sLORETA, standardized low-resolution brain electromagnetic tomography; STG, superior temporal gyrus; tDCS, transcranial directed current stimulation

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psychosis. For example, a modest effect size of MMN impairments was observed in subjects at clinical high risk for psychosis who later developed into psychosis (Erickson et al., 2016). As a result of these findings, there has been an increased interest in understanding how to modulate MMN, as it may serve as a possible therapeutic intervention in a clinical setting (Chen et al., 2014; Erickson et al., 2016).

Non-invasive brain stimulations, including repetitive transcranial magnetic stimulation (rTMS) and transcranial directed current stimulation (tDCS), can be used to regulate specific neural activities (Daskalakis, Christensen, Fitzgerald, & Chen, 2002; Romei, Thut, & Silvanto, 2016). Presently, there are a few studies that have attempted to manipulate MMN activity using these non-invasive tools (Hansenne, Laloyaux, Mardaga, & Anseau, 2004; Oshima et al., 2016). In one such study, low-frequency (1 Hz) rTMS over the left parietal cortex decreased MMN amplitudes responding to the right-ear stimuli in healthy controls (Oshima et al., 2016). Reduced MMN activities were also observed after delivering anodal tDCS over the right inferior frontal cortex, left dorsolateral prefrontal cortex or left auditory cortex (Chen et al., 2014; Impey, De la, & Knott, 2016; Weigl, Mecklinger, & Rosburg, 2016). These studies provide encouraging evidence that non-invasive transcranial brain stimulations can influence pre-attentive processing that is reflected by MMN activity. However, in these studies, magnetic or electrical stimulations were delivered to various regions, such as the left dorsolateral prefrontal cortex (Weigl et al., 2016), right inferior frontal cortex (Chen et al., 2014), left parietal cortex (Oshima et al., 2016) and left auditory cortex (Impey et al., 2016). The stimulation locations were relatively large and were usually chosen according to the 10-10 international system for EEG electrode placement, which is not precise (Impey & Knott, 2015). The limitation of identifying the target for stimulation may influence the modulation effects on MMN. Thus, it is essential to develop a precise strategy of manipulating MMN activity, which may be achieved by individualized neuroimaging-guided rTMS modulations.

Moreover, multiple auditory MMN activities can be elicited by various deviant features, including frequency, intensity, and duration (Garrido et al., 2009). The generators of MMN, which are dependent on the acoustic features, have different source localizations in the auditory cortex (Molholm et al., 2005). For example, Molholm et al. found that duration-related MMN (dMMN) activity was localized within the right superior temporal gyrus (STG), which is posterior and lateral to the origins for frequency-related MMN (fMMN) activity (Molholm et al., 2005). In addition, dMMN and fMMN altered in different manners during the progress of disease (Erickson et al., 2016). fMMN impairments were commonly observed in chronic patients with schizophrenia, whereas deficits of dMMN and intensity-related MMN occurred in the earlier stage of first-episode patients or subjects at clinical high risk for psychosis (Todd et al., 2008; Umbricht & Kriljes, 2005). Rasser et al. examined the correlations between the loss of gray matter and reduced MMN amplitudes in schizophrenia (Rasser et al., 2011). dMMN reduction was associated with gray matter loss in the right Heschl's gyrus, while fMMN reduction was associated with gray matter loss in more widespread cortical regions not limited within the bilateral temporal cortex (Rasser et al., 2011). Since deviant features have influence on MMN generators, as well as the varied patterns of MMN deficits along with the disease progress, the attempts to modulate MMN activity should selectively and precisely target specific brain regions.

Precise rTMS intervention would pave the way for the manipulation of specific MMN activity based on the accurate MMN generator derived by a specific deviant. Thus, in the present study, we used an auditory oddball paradigm including both frequency and duration deviant sounds. With the aim of selectively modulating dMMN, rather than fMMN activity, a right posterior STG position was chosen as the target in concordance with Molholm's study (Molholm et al., 2005). Neuroimaging-guided intermittent theta burst stimulations (iTBS) were precisely delivered to individual right posterior STG. The iTBS paradigm is a new form of rTMS, and can produce long-term potentiation (LTP)-like

effect on the target cortex as conventional high-frequency rTMS protocol does (Blumberger et al., 2018; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). But iTBS has a longer after effect and can be delivered within a shorter time (Huang et al., 2005; Huang, Rothwell, Edwards, & Chen, 2008). We hypothesized that the neuroimaging-guided iTBS manipulation would modulate the dMMN activity but induce no obvious effect on fMMN activity.

2. Material and methods

2.1. Participants

Twenty-four graduate or undergraduate students were recruited from Shanghai Jiao Tong University by on-campus advertisements. Twenty-three subjects (15 females and 8 males) participated in both active and sham TMS experiments, whereas one male subject dropped out without participating in the sham TMS experiment. Three of the remaining 23 subjects were excluded from data analysis due to too many ocular artifacts. Finally, 20 subjects (14 females and 6 males, age (mean \pm S.D.): 24.45 \pm 2.24, years of education (mean \pm S.D.): 16.45 \pm 1.00) completed both active and sham TMS experiments with good-quality EEG data were included in the following analysis. All participants were screened by a psychiatrist (T. Zhang). None of them had a personal or family history psychiatric disorders, a history of any substance or alcohol abuse, severe neurological or physical disease. All subjects had no contraindication for MRI or TMS procedures (i.e., any foreign metallic objects in their head or stimulator in their body). The experimental protocol was approved by the Ethics Committee in Shanghai Mental Health Center (SMHC) in compliance with the Helsinki Declaration. Written informed consent was obtained from each participant before the experiments. Each participant was compensated for their participation.

Each subject participated experiments twice, one of active iTBS stimulation and the other of sham stimulation. The order of receiving active and sham iTBS stimulations was counterbalanced across the participant pool. The two stimulations were separated at least 1 week with mean intervals of 18.95 (S.D. = 12.83) days. A questionnaire was used to evaluate side effects after either active or sham TMS stimulations. No side effects of any seizure, syncope, local pain, headache or hearing problem were reported.

2.2. Experimental procedure

For each experiment, the procedure included: (1) acquisition of individual structural T1-weighted images; (2) the first examination of individual resting motor threshold (MT) and motor evoked potential (MEP); (3) the first MMN paradigm before stimulation; (4) neuroimaging-guided TMS modulation with active iTBS or sham stimulations; (5) the second MMN paradigm after stimulation; and (6) the second examination of MT and MEP.

2.2.1. MRI data acquisition

To localize an individual TMS target accurately, structural T1-weighted images were obtained on a Siemens 3.0-T Verio MRI scanner (MR B17, Siemens AG, Erlangen, Germany) with a 32-channel head coil in SMHC. To minimize head motion, foam padding was placed around each subject's head. T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence with repetition time (TR) = 2530 ms, echo time (TE) = 3.65 ms, field of view (FOV) = 256 mm, voxel size = 1 mm \times 1 mm \times 1 mm, 224 coronal slices, slice thickness = 1 mm and flip angle = 7°.

2.2.2. Precise locations for posterior STG in TMS modulation

We identified the individual TMS target of the right posterior STG using LOCALITE TMS Navigator (LOCALITE GmbH, Scholoss

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