International Journal of Psychophysiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Enhanced theta-gamma coupling associated with hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression

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ARTICLE INFO

Keywords:
Depression
Hippocampus and prefrontal network
Neuroplasticity
Theta-gamma coupling
rTMS

ABSTRACT

The underlying mechanism of repetitive transcranial magnetic stimulation (rTMS) effects on cognition has not been fully examined. Previously, we have reported the left hippocampal volume increase and theta-gamma coupling (TGC) enhancement associated with working memory improvement following rTMS in depression. This study was aimed to examine whether there is a structure-function relationship in hippocampal neuroplasticity induced by prefrontal rTMS. Thirty-one patients with major depression underwent longitudinal MRI scans and resting-state EEG recordings with the 10–20 system using averaged ear-lobes reference, following 10 sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex. Pearson's correlation analyses were applied for the longitudinal changes among the left and right hippocampal volumes as measured by manual volumetry, theta and gamma spectral powers, and TGC as measured by resting-state EEG. The analyses demonstrated that the left hippocampus volume increases correlated with TGC increases at the left central area ($r = 0.576$, $p = 0.001$, $N = 31$), whereas no significant correlations were observed among changes of right hippocampal volume, right central TGC, bilateral gamma or theta powers. These finding suggests structure-function relationship in rTMS-induced neuroplastic changes mediated through the hippocampus and prefrontal network at the stimulated side. Therefore, high-frequency prefrontal rTMS may exert its cognitive effect through the hippocampal structural-functional neuroplasticity.

1. Introduction

Major depression is one of the debilitating forms of mental illnesses and the second largest global burden of disease as indexed by the DALYs (Ferrari et al., 2013; Whiteford et al., 2013), especially in the context of treatment resistance. Recently, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment option for treatment-resistant depression and its therapeutic effect has been demonstrated in well over 100 clinical trials (McClintock et al., 2017; Milev et al., 2016). However, the underlying biological mechanisms of action of rTMS, especially in terms of its cognitive effects, have not been fully elucidated (Martin et al., 2017).

Specifically, it is known that hippocampal and prefrontal cortex interactions play an important role in cognitive functioning and disruptions in these interactions may contribute to the pathophysiology in various psychiatric diseases including depression (Godsil et al., 2013; Uhlhaas and Singer, 2012). Moreover, electrophysiological studies in rats have shown that neural activities between the hippocampus and the prefrontal cortex are often synchronized in time and the interaction of both neuroanatomical structures are required to coordinate the appropriate cognitive functions (Gruart et al., 2015; Jones and Wilson, 2005). In addition, a functional MRI study in humans has demonstrated that hippocampus and DLPFC coupling may represent a systematic mechanism that implements working memory (Bahner et al., 2015).

The hippocampus has distinct electrophysiological characteristics of the theta-phase and gamma-amplitude coupling (TGC), which means the gamma oscillations (30-100 Hz) onto the theta rhythms (5–10 Hz: typically a 4–8 Hz band) (Marmpena et al., 2016; Scheffer-Teixeira and

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https://doi.org/10.1016/j.ijpsycho.2018.07.004
Received 29 April 2018; Received in revised form 3 July 2018; Accepted 5 July 2018

Tort, 2016). Furthermore, the TGC is thought to play an important role in learning and memory associated with neuroplasticity in the hippocampal-cortical network, facilitating cognitive functioning (Colgin, 2015; Tamura et al., 2017). For example, a rat study using a chronic stress model demonstrated that the TGC between hippocampus and prefrontal cortex was disrupted, which resulted in the impairment of synaptic plasticity in this pathway (Zheng and Zhang, 2015). Further, in the same rat model of chronic stress, between hippocampus and prefrontal cortex, the theta phase coupling was decreased with the injection of dopamine D1 receptor antagonist while the gamma oscillations increased with the 5-HT1A receptor agonist (Xu et al., 2016). Thus, monoaminergic antidepressants may exert its pro-cognitive effect through the potentiation of synaptic plasticity mediated by dopaminergic and serotonergic modulations in the hippocampal and prefrontal network.

Our group has previously reported that high-frequency left dorsolateral prefrontal cortex (DLPFC) rTMS induced a significant increase of TGC on resting-state EEG at the C3 electrode site over the left central area in patients with major depression, and further this increased TGC was significantly associated with cognitive improvement as assessed by the Wisconsin Cord Sorting Test (WCST) following rTMS treatment (Noda et al., 2017). Furthermore, rTMS treatment using the same protocol induced a lateralized hippocampal volume increase as measured by MRI on the left side that was the stimulated site of rTMS (Hayasaka et al., 2017). In our previous study, there was no significant relationship between MRI hippocampal volume changes and cognitive outcomes following rTMS in this population, however, the relationship between hippocampal volumetric changes and TGC has not been previously evaluated.

Therefore, in the present study, we hypothesized that the left hippocampal volume increases in depression induced by high-frequency left DLPFC rTMS would be associated with functional neuroplasticity, which is relevant to the cognitive executive functioning, as indexed by TGC on resting-state EEG. We examined the relationship between changes of hippocampal structural changes and TGC, gamma and theta powers by rTMS treatment in patients with depression using our previous datasets to elucidate the underlying therapeutic mechanism of cognitive improvement associated with rTMS treatment in major depression.

2. Material and methods

2.1. Participants

Thirty-one medicated patients with major depression diagnosed with the ICD-10 (43 ± 11 (mean ± S.D.) years; 21 males) were included in the present study (Noda et al., 2017). There was no special reason for the untypical ratio of male to female patients with depression who participated in this study. All participants were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) prior to study participation and they had no neuropsychiatric comorbidities and no history of neurological disorders, epilepsy, or substance abuse. Demographic and clinical data are shown in Table 1. Written informed consent was obtained from each participant. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kanagawa Psychiatric Center.

2.2. Study design

High-frequency left DLPFC rTMS was administered to all patients over two weeks from Monday to Friday (i.e., 10 sessions in total) in the context of an open-label study (Noda et al., 2013). Before and after the acute course of rTMS, all patients underwent clinical and cognitive assessments using the Hamilton Rating Scale for Depression (HAM-D_{17}) and the Wisconsin Card Sorting Test (WCST). Further, MRI scan and resting-state EEG were measured in all patients at the same time point before and after an acute course of rTMS treatments (Hayasaka et al., 2017; Noda et al., 2017). Although all patients were taking antidepressant medications during the study, medications were fixed during the study period to avoid the potential influence of medication changes on the longitudinal cognitive and biological measure changes.

Table 1
Demographic, clinical, cognitive, and medication data.

(N = 31)	Patients (mean ± S.D.)
Age (years old)	42.8 ± 10.8 (29–62)
RMT (%) of participants in this study	82.2 ± 10.6 (56–94)
%RMT (%) used in this study	95.1 ± 7.9 (88–108)
Baseline HAMD 17-item	15.3 ± 4.6 (10–25)
Two weeks HAMD 17-item	6.9 ± 4.7 (1 − 13)
Baseline WCST (number of error)	21.7 ± 9.7 (8–48)
Two weeks WCST (number of error)	12.9 ± 7.1 (5–32)
Imipramine equivalent dose (mg/day)	166 ± 101 (0–350)
Chlorpromazine equivalent dose (mg/day)	100 ± 126 (0–400)
Diazepam equivalent dose (mg/day)	10.3 ± 5.5 (0 − 22)

RMT: resting motor threshold; HAMD: Hamilton Rating Scale for Depression; WCST: Wisconsin Card Sorting Test. %RMT was not set to the specific percentage of RMT but adjusted according to the tolerability for each participant, which resulted in approximately 90–100% RMT in this study.

2.3. rTMS procedure

rTMS treatment was conducted with a Magstim Super Rapid system (The Magstim Company Ltd., Whitland, UK) using a 70-mm figure-of-eight coil with a special air-cooling system. Stimulation parameters of rTMS were 25 trains of 2 s duration at 20 Hz with inter-train intervals of 28 s, 1000 pulses per session, which was previously described in our study (Noda et al., 2013). This treatment protocol was relatively weak compared to the FDA approved standard protocol. However, this is because when this study was conducted, we had to follow the safety guidelines of the Japanese Society of Clinical Neurophysiology, which limited the number of stimulation pulses to the maximum of 5000 per week. The left DLPFC target was defined as the center of the middle frontal gyrus (mainly Brodmann area 46). For each participant, an MRI-guided real-time ultrasound-based navigation (BrainVoyager TMS Neuronavigator, Brain Innovation; Maastricht, the Netherlands and Zebris Medical GmbH; Isny im Allgäu, Germany) was used in order to be able to accurately place the TMS coil at the target site. The individual resting motor threshold was determined as the lowest stimulus intensity produced in the relaxed first dorsal interosseous muscle. The stimulus intensity was set ranging from approximately 90% to 100% of the resting motor threshold, depending on the tolerability of a participant.

2.4. MRI acquisition and processing

The MRI was scanned with a 1.5-Tesla Philips scanner (Intera NovaDual, Philips; Amsterdam, the Netherlands) at the Kanagawa Cardiovascular and Respiratory Center in Yokohama, Japan. Sagittal series of contiguous 1.0-mm images (echo time = 5 ms, repetition time = 35 ms, repetition = 1, nutation angle = 45°, field of view = 24 cm, acquisition matrix = 256 × 256 × 200 or more, voxel dimension = 0.9375 × 0.9375 × 0.9375 mm) were created by a 3-D Fast Field Echo acquisition sequence. The images were realigned using the line between the anterior and posterior commissures and the sagittal sulcus to correct for the head tilt and resampled into isotropic voxels (0.9375 mm^3). Structural MRI volume was analyzed using the manual tracing method (see details in (Hayasaka et al., 2017).