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Potentiation of quantitative electroencephalograms following prefrontal repetitive transcranial magnetic stimulation in patients with major depression

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ABSTRACT

The long-lasting effects of repetitive transcranial magnetic stimulation (rTMS) on electroencephalogram (EEG) activity are not clear. We aimed to investigate the cumulative rTMS effects on EEG and clinical outcomes in patients with major depression. Twenty-five patients with medication-resistant depression underwent 10 daily rTMS sessions over the left dorsolateral prefrontal cortex. We measured resting EEG and spectrum-power before and after the rTMS course. Clinical efficacy was evaluated with the Hamilton's Depression Rating Scale (HAM-D) and Wisconsin Card Sorting Test (WCST). In an ANOVA model, including all prefrontal electrodes, post hoc analyses revealed significant time effects on the theta ($F_{1,24}$ = 7.89, P = 0.010; +43%), delta ($F_{1,24}$ = 6.58, P = 0.017; +26%), and alpha ($F_{1,24}$ = 4.64, P = 0.042; 31%) bands without site specificity. Clinical correlations were observed between F4 alpha power increases and improvements in HAM-D retardation, F3 alpha power increases and improvements of the absolute changes in perseveration and error number on the WCST, and C3 and C4 theta power increases and improvements of the percent change in perseveration and error number on the WCST following rTMS. Consecutive prefrontal rTMS could induce long-lasting EEG potentiations beyond the aftereffects, resulting in improved cognitive and depressive symptoms.

1. Introduction

Transcranial magnetic stimulation (TMS) is used for noninvasive human brain stimulation to study cognitive function in healthy subjects and the pathophysiology of disease. Repetitive TMS (rTMS) is a neuromodulation method that has been used therapeutically in neurology, psychiatry, and rehabilitation (Nahas et al., 1999; Kobayashi and Pascual-Leone, 2003; Paus and Barrett, 2004; Rossi and Rossini, 2004; Miniussi et al., 2005; Ridding and Rothwell, 2007; Padberg and George, 2009). This method promotes changes in neuronal circuit excitability in facilitative and/or inhibitory ways depending on the protocol. The effects of rTMS outlast the stimulation period and are therefore not limited to the stimulated cortex but spread across neuronal circuits as remote effects (Walsh and Cowey, 2000; Jing and Takigawa, 2000; Robertson et al., 2003; Hallett, 2007; Guse et al., 2010). Moreover, rTMS induces short-lasting aftereffects on electromyogram (EMG) and electroencephalogram (EEG) activities because of its cumulative effects (Bäumer et al., 2003; Siebner and Rothwell, 2003; Thut and Pascual-Leone, 2010). Therefore, a combination study of rTMS and EEGs is used to evaluate rTMS effects on brain function, especially in nonmotor regions (Paus et al., 2001; Ilmoniemi and Kičić, 2010; Miniussi and Thut, 2010).

In most combination studies of rTMS and EEGs, rTMS has been applied to the primary motor cortex (M1) to in healthy subjects

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; ED, equivalent dose; EEG, electroencephalography; E-LTP, early phase long term potentiation; EMG, electromyography; FDI, first dorsal interosseous; FFT, fast Fourier transform; Fm-theta, front midline theta; HAM-D, Hamilton's Rating Scale for Depression; HFS, high frequency stimulation; ICD-10, international classification of disease 10th; LORETA, low resolution brain electromagnetic tomography; LTP, long term potentiation; L-LTP, late phase-long term potentiation; MEP, motor evoked potential; M1, primary motor cortex; MRI, magnetic resonance imaging; MSO, maximum stimulator output; qEEG, quantitative electroencephalography; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; WCST, Wisconsin Card Sorting Test.

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(Paus et al., 2001; Fuggetta et al., 2005). These studies usually involve intermittent short rTMS trains to analyze EEG activity during and immediately after each train (Fuggetta et al., 2005, 2008; Ilmoniemi and Kičić, 2010; Miniussi and Thut, 2010). A single rTMS session over M1 induces transient and short-lasting alpha power increases in background EEG activity (Fuggetta et al., 2005, 2008; Brignani et al., 2008; Choi et al., 2011; Veniero et al., 2011). Short-lasting theta power increases in the region around the stimulation site are aftereffects of a single session of 1-Hz rTMS over the dorsolateral prefrontal cortex (DLPFC) (Schutter et al., 2001). Transient delta power increases have been shown after a single 10-Hz rTMS session over the left DLPFC in healthy subjects (Griskova et al., 2007), and significant beta power increases have been shown after a single 5-Hz rTMS session over M1 (Fuggetta et al., 2008). However, little is known about the prefrontal rTMS effects on EEG activity (Spronk et al., 2008). Several studies have explored transient (ms to s) and/or short-lasting (within ~70 min) aftereffects after a single rTMS session, while long-lasting changes in resting EEG activities that are elicited by multiple rTMS sessions have not been widely studied (Thut and Pascual-Leone, 2010). Spronk et al. have investigated changes in quantitative EEG (qEEG) after rTMS (up to 21 sessions; to the left DLPFC) in patients with depression, and qEEG power changes were not observed. However, a trend-level delta power increase occurred in the right frontal region (Spronk et al., 2008).

Long-term potentiation (LTP), which is involved in synaptic plasticity is the most important factor for rTMS-induced neuromodulation (Cohen et al., 1998). It is usually classified into early (E-LTP) and late (L-LTP) phases, depending on protein synthesis and the duration of maintained potentiation (Shors and Matzel, 1997; Kandel, 2001; Reymann and Frey, 2007). E-LTP usually lasts about 2 h and corresponds to the aftereffects of a single rTMS session, whereas L-LTP exceeds several hours, which is similar to the long-lasting changes in EEG activity induced by consecutive rTMS sessions (Bengtson et al., 2010). Several lines of evidences strongly suggest an association between rTMS-induced aftereffects and synaptic plasticity induction (Esser et al., 2006; Hoogendam et al., 2010). Those studies have shown a close association between motor learning skills and rTMS-induced power changes in motor cortex EEG, suggesting that the latter may result from neuroplastic changes, such as LTP.

In this study, we investigated the cumulative effects of consecutive prefrontal rTMS sessions on EEG activities and clinical outcomes in patients with major depression. We hypothesized that correlations between qEEG spectral power potentiations and clinical findings after rTMS sessions imply L-LTP-like effects, which are maintained for several hours to days (Kandel, 2001; Reymann and Frey, 2007). Furthermore, we postulated that significant theta power changes after prefrontal rTMS would be associated with functional modulation of frontal midline theta (Fm-theta) activities (Asada et al., 1999; Romero et al., 2008), which originate from the medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC), and which function to monitor consecutive mental tasks (Inouye et al., 1994; Ishii et al., 1999; Onton et al., 2005; Tsujimoto et al., 2006; Mitchell et al., 2008).

2. Materials and methods

2.1. Subjects

Twenty-five patients with medication-resistant major depression [17 men, 8 women; mean ± standard deviation (SD) age, 44.6 ± 10.7 years] participated in this open-label study. Depressive episodes of major depression were diagnosed by psychiatrists with ICD-10 at study entry, and all subjects answered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to confirm their diagnoses after enrollment. Medication-resistant depression was defined as a case not responding to more than 2 antidepressants over at least 6 months and persisting in a depressive state (Hamilton's Rating Scale for Depression 17-item version [HAM-D 17-item] score ≥8). However, since several patients have indicated a mild level of depression assessed by HAMD 17-items before starting rTMS treatment in our study, medication-resistant is used to indicate the patients who have not reached a complete remission with medications. Therefore, the majority of patients have demonstrated a persistent mild depressive state in the context of medication-resistant depression in this study.

Table 1
Demographic, clinical outcome and medication data.

Population (N = 25)	Major depressive disorder
Age (y)	44.6 ± 10.7 (y)
Gender M/F	17/8
Age of onset (y)	37.0 ± 11.7
Duration of disease (y)	7.6 ± 3.6
RMT (%)	78.2 ± 9.4 MSO (N = 22)
TMS intensity (%)	76.9 ± 6.8 MSO (N = 25)
% RMT	97.8 ± 5.9 (N = 22)
Baseline-HAMD	14.2 ± 6.5
Two week-HAMD	6.4 ± 4.5
Medication	*Equivalent dose* (mg/day)
Antidepressants	192 ± 122 (*Imipramine-E.D.*)
Antipsychotics	67 ± 108 (*Chlorpromazine-E.D.*)
Benzodiazepines	10.2 ± 8.6 (*Diazepam-E.D.*)

RMT, resting motor threshold; HAM-D, Hamilton's Depression Rating Scale.
The data represent means ± standard deviation (SD); E.D., equivalent dose.

No patients had psychiatric comorbidities and they were diagnosed with monopolar depression (18 patients), bipolar I depression (2 patients), or bipolar II depression (5 patients). The patients had no history of neurological disorders, epilepsy, or substance abuse and did not meet the exclusion criteria for TMS (head trauma, pacemakers, or pregnancy). Table 1 lists the demographic data. All subjects provided written informed consents in accordance with the Declaration of Helsinki, and the study was approved by the Local Ethics Committee of Kanagawa Psychiatric Center.

2.2. Experimental design

The experimental design was an open-label study (Fig. 1). In this study, the subjects underwent 10 daily rTMS sessions over the left DLPFC for 12 days, with one daily rTMS session conducted Monday to Friday for 2 weeks. Medication information is summarized in Table 1. The average *imipramine*-equivalent (antidepressants), *chlorpromazine*-equivalent (antipsychotics), and *diazepam*-equivalent (benzodiazepines) doses were (mean ± SD) 192 ± 122, 67 ± 108, and 10.2 ± 8.6 mg/day, respectively (Bollini et al., 1999; Woods, 2003; Greenblatt et al., 1988). During the rTMS series, medications were not changed, and psychotherapy, occupational therapy, or other treatments were not administered.

The stimulation parameters were 1000 pulses per session, 25 trains of 40 stimuli at 20 Hz with a 28-s intertrain interval. Therefore, the total number of stimuli for each subject was 10,000 pulses in 10 sessions. The left DLPFC stimulation site was determined with an ultrasound-based navigation system (zebris Medical GmbH, Isny im Allgäu, Germany; BrainVoyager TMS Neuronavigator, Brain Innovation B.V., The Netherlands).

Clinical evaluations with the HAM-D 17-item and the Wisconsin Card Sorting Test (WCST) were conducted before and after the consecutive rTMS sessions. The 2-component model of HAM-D consisted of the retardation and agitation subscales, and the retardation subscale comprised items 1, 2, 3, 4, 7, and 8 (Angst et al., 1993).