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# Different responses to facilitatory rTMS according to BDNF genotype

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HIGHLIGHTS

- High-frequency rTMS significantly induces the facilitation of cortical excitability regardless of brain-derived neurotrophic factor (BDNF) genotype.
- BDNF genotype influence rTMS-induced plasticity based on the rTMS intensity.
- Our findings suggest that the individual rTMS strategy will be needed according to the brain-derived neurotrophic factor genotype.

ABSTRACT

*Objective:* To investigate whether there is a relation between the plasticity induced by different intensities of facilitatory rTMS with different intensities and brain-derived neurotrophic factor (BDNF) genotype.
*Methods:* Forty healthy volunteers (14 men, mean age 27.3 years) were enrolled. All participants received three high-frequency rTMS applications in random order over the non-dominant primary motor cortex with more than a 24-h washout period: 1st condition, rTMS with sub-threshold intensity; 2nd condition, rTMS with supra-threshold intensity; and 3rd condition, sham rTMS. Cortical excitability was assessed before and after rTMS using motor-evoked potentials (MEPs). Data were analyzed using the BDNF genotype.
*Results:* Twelve, 19, and 9 participants were classified into Val/Val, Val/Met, and Met/Met groups, respectively. In each group, there were significant increases in the amplitude of MEPs after 1st and 2nd conditions ($P < 0.05$), but not after 3rd condition. In Val/Val group, the increase ratio of MEPs' amplitude after 2nd condition was significantly higher than 1st condition ($P < 0.05$). However, no significant amplitude differences in Val/Met and Met/Met groups were observed after 1st and 2nd conditions.
*Conclusions:* High-frequency rTMS induces the facilitation of cortical excitability regardless of BDNF genotype. BDNF genotype might influence on different responses of plasticity based on the rTMS intensity.
*Significance:* BDNF genotype is one of influence factors on the plasticity after the facilitatory rTMS.


## 1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) refers to the application of regularly repeated stimuli to a single scalp position. rTMS has both inhibitory and facilitatory effects on cortical excitability. These modulatory effects of rTMS appear dependent on the stimulation intensity, duration, and particularly the

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stimulation frequency (Maeda et al., 2000a; Pascual-Leone et al., 1998). The term high-frequency rTMS is used when the stimulation rate is more than 1 Hz, and low-frequency rTMS is used when the stimulation rate is 1 Hz or less. Many studies assume that high-frequency rTMS has a facilitatory effect and low-frequency rTMS has an inhibitory effect. Through these cortical modulating effects, the past year has seen the publication of a remarkable number of papers on the potential therapeutic influences of rTMS on neuropsychiatric disorders. However, individual responses to rTMS are highly variable, even in healthy subjects. A number of factors have already been described that contribute to this variability, such as brain lesions (Ameli et al., 2009), the menstrual cycle (Inghilleri et al., 2004), subjects' age (Muller-Dahlhaus et al., 2008), the time of day (Sale et al., 2008), pharmacological treatments (Fregni et al., 2006), and genetic factors (Missitzi et al., 2011).

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and has been reported to modulate N-methyl-D-aspartate receptor (NMDAR)-dependent long-term potentiation (LTP) and long-term depression (LTD)-related processes in animal cortexes (Aicardi et al., 2004; Figurov et al., 1996; Woo et al., 2005). Furthermore, a single nucleotide polymorphism has been identified in the human BDNF gene at codon 66 (Val66Met), the replacement of Val66 with Met66 has been reported to disrupt cellular processing, trafficking, and the activity-dependent secretion of BDNF (Egan et al., 2003). The Met allele has also been associated with poorer episodic memory and lower hippocampal (Egan et al., 2003) and prefrontal cortical activity (Soliman et al., 2010).

Previous studies have suggested that the BDNF Val66Met polymorphism may influence the synaptic plasticity (Cheeran et al., 2008; Kleim et al., 2006). However, some studies have shown that the presence of the Val66Met BDNF polymorphism dose not reliably predict responsiveness in rTMS induced plasticity (Li Voti et al., 2011; Mastroeni et al., 2013). Also, there were few studies about response of different rTMS intensities in terms of cortical facilitation according to BDNF genotype. This study aims to investigate whether there is a relation between the plasticity after the facilitatory rTMS with different intensities and BDNF genotype.

## 2. Methods

### 2.1. Participants

Forty healthy volunteers (14 men, mean age 27.3 years) were recruited for this study after providing written informed consent. Inclusion criteria were age (20–70 years), and the absence of neurological and psychiatric diagnoses. None of the subjects had epilepsy, chronic illnesses, or metallic intracranial implants. The methods were approved by the Samsung Medical Center Institutional Review Board (2011-06-042) and this study conformed with the 2013 WMA Declaration of Helsinki. Also, this study were undertaken with the understanding and written consent of each subject.

### 2.2. Experimental design

All participants received three conditions of rTMS in random order over the non-dominant M1 (Fig. 1). The first condition was high-frequency rTMS (10 Hz) with sub-threshold intensity (90% of resting motor threshold (rMT)); the second condition was high-frequency rTMS (10 Hz) with supra-threshold intensity (110% of rMT); and the third condition was sham rTMS. Participants' non-dominant hemisphere was determined using the Edinburgh Handedness Inventory. All participants underwent the following: (1) Cortical excitability with motor-evoked potentials (MEPs) was assessed before and after rTMS with a total of 1000 stimuli for 20 min. (2) Side effects after rTMS were assessed using a Likert scale (0–10). (3) Three conditions of rTMS applied in random order with a washout period of more than 24 h (4) Data were analyzed with respect to BDNF genotype, that is by comparing Val/Val vs. Val/Met vs. Met/Met groups.

### 2.3. Cortical excitability measurement

MEPs were assessed by single magnetic stimulations at 120% of the rMT over the non-dominant M1 using a 70-mm figure-of-eight coil. During the experiments, subjects sat comfortably in an armchair with their eyes open. A Synergy electromyography/evoked potentials system (Medelec Co. Ltd., Kingswood, Bristol, UK) was used to record and monitor the activity of the contralateral first dorsal interosseus (FDI) muscle. Single-pulse TMS was applied over the non-dominant M1 with a Magstim Rapid2® stimulator (Magstim Co. Ltd., Spring Gardens, Whitland, Carmarthenshire, Wales, UK) equipped with a 70-mm figure-of-eight coil. The coil was held tangentially to the scalp, with the handle pointing backward and laterally at 45° from the mid-sagittal line. Using TMS, the optimum position ("the hot spot") was defined as the site where TMS induced MEPs of maximum peak-to-peak amplitude in the contralateral FDI muscle. rMT was defined as the lowest stimulus intensity able to evoke MEPs of at least 50 μV peak-to-peak amplitude in five out of 10 consecutive trials. Five sweeps of the MEPs at 120% of the rMT were collected, and the mean amplitude and latency of the MEPs were calculated (Rossini et al., 1994).

### 2.4. Side effect assessments

After each rTMS, we assessed its known side effects of rTMS (Wassermann et al., 1996). The nine major side effects assessed were anxiety, fear, headache, tinnitus, dizziness, hearing loss, fainting, nausea, and vomiting. Participants rated the intensities of these side effects after rTMS using a numeric rating scale (score: 0–10) (Liu and Aitkenhead, 1991), and total side effect intensities were calculated by summing scores.

### 2.5. rTMS intervention

rTMS was delivered on the scalp over the non-dominant M1 in accordance with safety recommendations (Wassermann et al., 1996) using a figure-of-eight shaped coil connected to a Magstim Rapid® stimulator with two booster modules (Magstim Co. Ltd., Spring Gardens, Whitland, Carmarthenshire, Wales, UK). The coil was held tangentially to the scalp with the handle pointing backward and laterally at 45° from the mid-sagittal line to stimulate the motor cortex. All participants received three conditions of rTMS in random order, with more than 24 h of washout period. The 1st condition was high-frequency rTMS (10 Hz) with sub-threshold intensity (90% of rMT) over a period of 5 s. The 2nd condition was high-frequency rTMS (10 Hz) with supra-threshold intensity (110% of rMT) over a period of 5 s. Twenty trains of rTMS were applied at 55-s inter-train intervals; therefore, a total of 1000 stimuli were applied during 20 min of each rTMS session. The 3rd condition was sham rTMS; sham stimulation was performed at the same site and at the same frequency and intensity as that of real rTMS. The MEPs was undertaken immediately following cessation of each rTMS train.

### 2.6. BDNF genotyping technique

A sample of each subject's blood was genotyped for the BDNF Val66Met polymorphism. Whole blood was placed into EDTA tubes and DNA was extracted using standard procedures. Polymerase