Study of Effects on Event-Related Potentials by Repetitive Transcranial Magnetic Stimulation to the Cerebral Cortex : Effects of sub-threshold in magnetic stimulation

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Summary

Transcranial magnetic stimulation (TMS) device developed in 1985 by Barker et al. does not produce such painful discomfort (Barker et al., 1985a). This method of stimulating the cerebral cortex uses noninvasive stimulation based on a pulsed magnetic field, and this magnetic field pulse is not attenuated by the high impedance of the scalp or the skull (Barker et al., 1985b). After the introduction of TMS by Barker et al. in 1985, repeated stimulation by TMS (repetitive transcranial magnetic stimulation: *r*TMS) has become very useful in cerebral nerve physiology studies. *r*TMS was introduced into treatment by Pascual-Leone et al. in 1987 (Pascual-Leone et al., 1996). Many previous studies have reported that these technologies, such as TMS or *r*TMS, might alter cortical excitability (whether in an inhibitory or facilitatory fashion). Individual optimal magnetic stimulation parameters may be necessary for the consistency of the modulation of cortical excitability across participants by magnetic stimulation (Pascual-Leone et al., 1998). Moreover, the effect on cortical excitability may vary in a complex way depending on the particular combination of stimulation parameters. In the future, a study to clarify the relationship between the magnetic stimulation parameters and changes in cortical excitability alteration is necessary.

TMS has been widely used in the study of motor function along with the simultaneous measurement of MEPs (Barker 1989; Mano et al., 1993a, b). This rapid growth has led to new technical developments such as improved TMS and *r*TMS stimulus coils, and noninvasive dynamic functional brain imaging. Moreover, the combination of TMS and functional brain imaging methods, such as positron emission tomography (PET), electroencephalography (EEG) and functional magnetic resonance imaging (*f*MRI) has shown it to be an effective technique for many studies of the brain. Therefore, TMS and *r*TMS have become indispensable for the elucidation of human cerebral function (Kähkönen et al., 2005). In addition, a recent study that combined TMS with near-infrared spectroscopy (NIRS) has been reported (Aoyama et al., 2009; Kozel et al., 2009). In particular, the combination of EEG with TMS or *r*TMS is useful

in the instantaneous state investigation of alterations in cortical excitability, because EEG has superior temporal resolution (Kähkönen et al., 2005; Ilmoniemi et al., 2010).

The effect of rTMS on cognitive function has been investigated since 2000. Neurophysiological examinations have indicated that *r*TMS is safe from a cognitive function perspective (Triggs et al., 1999; Little et al., 2000). Several neurophysiological studies have indicated that the application of *r*TMS might actually improve cognitive processing (Pascual-Leone et al., 2000; Theoret et al., 2003). However, the mechanism of this improvement is not clear. Therefore, we are interested in the effects of *r*TMS on cognitive processing. It is thought that differences in magnetic stimulation parameters such as stimulation frequency, intensity or stimulation region induce different effects, but the details of these differences and the mechanism by which they produce this effect are unknown. Therefore, a detailed study of the impact on cognitive processing by TMS and *r*TMS is very important and necessary. However, suggestions for safe stimulation parameters were derived from *r*TMS applied to the motor cortex. In electrical stimulation, the threshold required to stimulate the motor cortex (MT) was lowest compared with the other regions (Penfield and Jasper, 1954); therefore it was thought that magnetic stimulation could be safely applied to non-motor areas. However, the relationship between motor and non-motor cortex has not been established in magnetic stimulation. In most of these studies, the intensity of magnetic stimulation to the motor cortex was the supra-motor threshold such as 100%MT to 120%MT. The intensity of magnetic stimulation to the non-motor cortex was 100 or 110%MT, except in the study by Evers et al. Previous studies did not mention this relationship (Rossi et al., 2009). In this situation, *r*TMS on the non-motor region may lack guidelines for utility or safety. Thus, the effects of *r*TMS on non-motor areas must be evaluated in detail.

Low-frequency *r*TMS of less than approximately 1 Hz decreases cortical excitability (inhibition), high-frequency *r*TMS of more than approximately 5 Hz increases cortical excitability (facilitation) (Pascual-Leone et al., 1994a; Chen et al., 1997; Berardelli et al., 1998). In many studies, effects lasting beyond the stimulation period have been confirmed, such as in the motor cortex (Hallett, 2000). The mechanism of this cortical

excitability alteration is unknown. In the one hypothesis of the modulation mechanism of cortical excitability, it is thought that a mechanism similar to long-term potentiation (LTP) and long-term depression (LTD) relate to the continuance of the effects of *r*TMS (Wang et al., 1996; Chen et al., 1997; Wassermann 1998; Hallett 2007).

The role of various stimulation parameters is unknown; however, the stimulation parameters of TMS and *r*TMS may be important in clinical applications (Klein et al., 1999). It is reported that using high-frequency *r*TMS induces an epileptic seizure (Pascual-Leone et al., 1992). If *r*TMS is used in a clinical setting, lower frequency *r*TMS may be safer (Klein et al., 1999).

Therefore, this study investigated magnetic stimulation parameters such as stimulation frequency, stimulation site and stimulation intensity. The effect of *r*TMS was evaluated by measuring the latency of the P300 component of the induced ERPs. This study also investigated the effects of magnetic stimulation on non-motor regions such as those associated with recognition.

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Chapter 1

History and Problems of with Magnetic Stimulation

History of and Problems with Magnetic Stimulation

1.1   Magnetic stimulation

Electrical stimulation of the cerebrum has been used since 1980. Transcranial electrical stimulation (TES) is a method that stimulates the cerebral cortex through the skull. However, the brain is protected electrically by the high impedance of the skull, scalp and hair (Merton et al., 1980). Therefore, the electrical stimulation causes pain and discomfort to participants. In addition, for electrical stimulation, localization to a target area of the cortex is not satisfactory. The cortex is stimulated by an electric current flowing between two electrodes. The electric current flows radially from an anode to a cathode. Therefore the placement of the stimulating electrode is very important. Technical reconsideration was needed to improve this situation.

Barker et al. developed transcranial magnetic stimulation (TMS) to solve several of the problems with TES, and showed that TMS could stimulate the brain directly (Barker et al., 1985a). TMS has the following advantages. First, magnetic stimulation is a noninvasive technology. Second, magnetic stimulation has few discomforts. Third, because the stimulation is not attenuated by the high impedance of the skull and scalp, the cortex is stimulated directly by TMS. Fourth, the magnetic stimulation coil over the skull can easily be moved to change the stimulation region. Fifth, stimulation of the deeper parts of the cerebrum is possible using TMS (Merton et al., 1982, Barker et al.,

1985ab, Hallett, 2000).

A short, high-current pulse flowing through the coil of wire, which is termed the magnetic coil, produces the magnetic field. The magnetic field occurs in a vertical direction from the coil's surface when placed on the scalp. Moreover, this magnetic field generates an eddy current in the brain. The direction of this eddy current is the opposite direction of the flow of the electric current in the magnetic coil. The generation of the eddy current is explained by Faraday's law of electromagnetic induction and Lenz's law. Cortical excitability may be modulated by an eddy current (***Figure I-1***) (Hallett, 2000, 2007; Ridding et al., 2007).
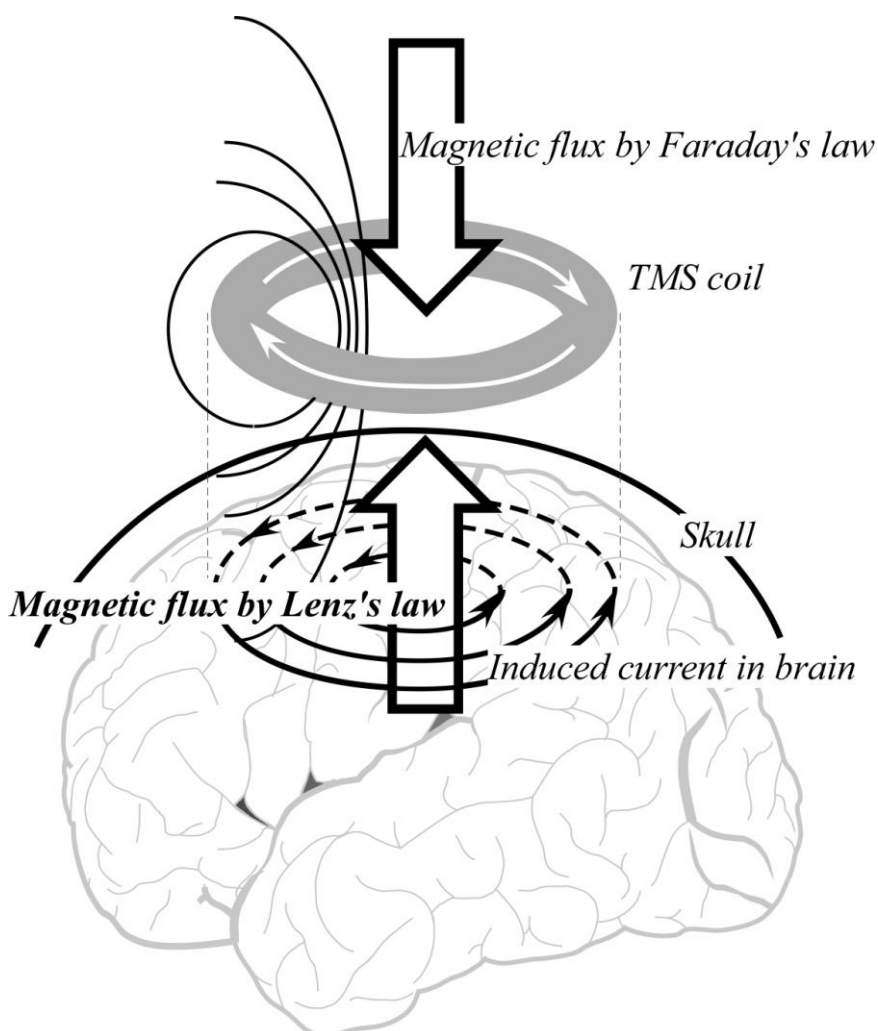
Figure I-1 Direction of current flow in a magnetic coil and the induced current in the brain (Ueno et al., 1988).

Various shapes for the magnetic coil have been introduced during technical development (***Figure I-2***). A round coil has been used since the development of TMS, and the strength of the magnetic field produced is relatively high, with a wide stimulation range. In contrast, a figure-eight-shaped coil has a more focal resolution of 5

Round coil
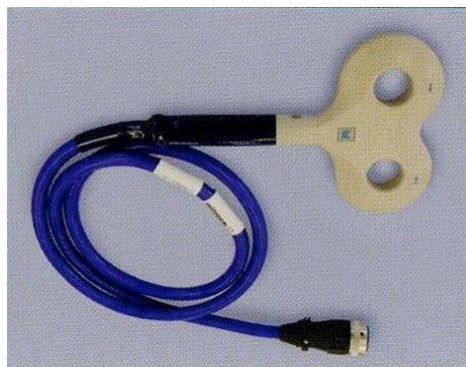
Figure-eight shaped coil

Figure-of-eight-shaped coil with the two

components at an angle

Figure I-2 The shape of the coil.

mm. Further, figure-eight-shaped coils composed of two round coils at an angle (under 180 degrees) produce more effective magnetic stimulation. In a round coil, the current intensity in the brain is strong in the circumference of the magnetic coil, while the current intensity in the brain is weak near the center of the coil, and there is no induced electric current under the center of the magnetic coil. In the figure-eight-shaped coil, the overlap of the coil raises the current intensity in the brain (***Figure I-3***) (Ueno et al., 1988; Ueno et al., 1990).
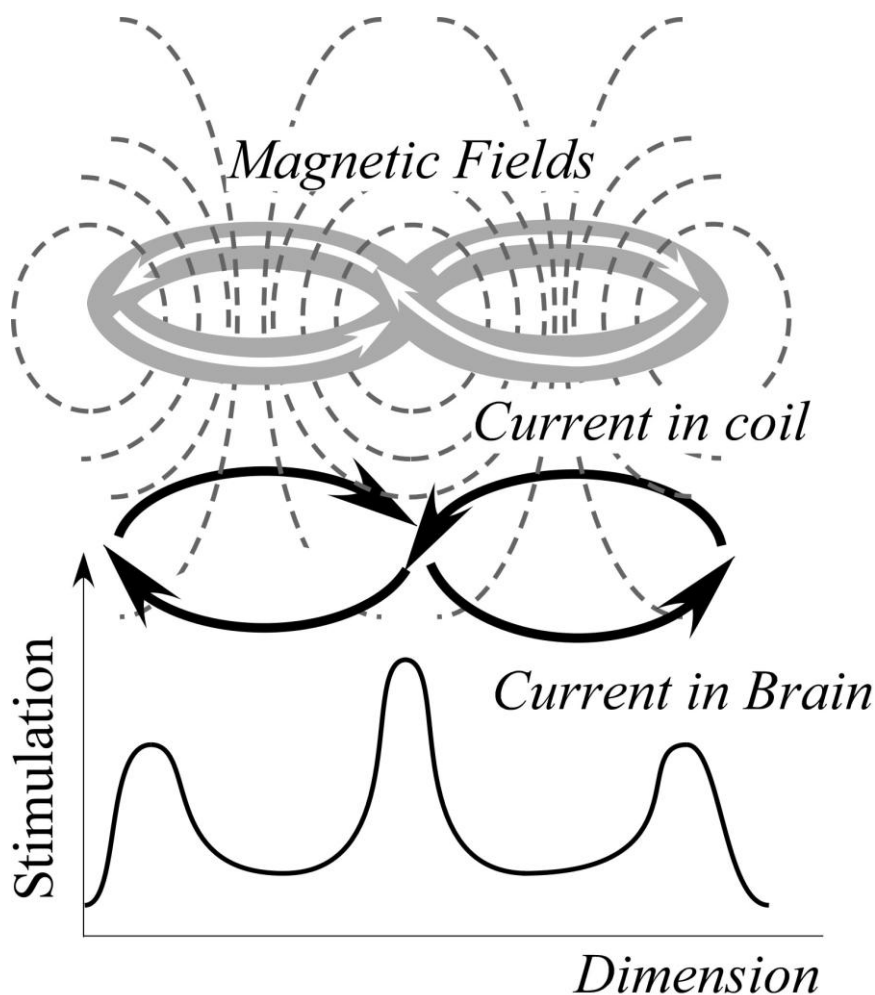
Figure I-3 Magnetic coil shape and resultant stimulus intensity in the brain (Ueno et al., 1990, 1988).

Motor evoked potentials (MEP) can be induced by TMS (***Figure I-4***) (Hasey, 2001; Mano et al., 1993a, b; Mano et al., 2003; Ridding et al., 2007). The muscle volley produced by TMS is based on the following mechanism. The eddy currents in the brain produced by the magnetic field induce excitability in the cerebral inter-neurons. This
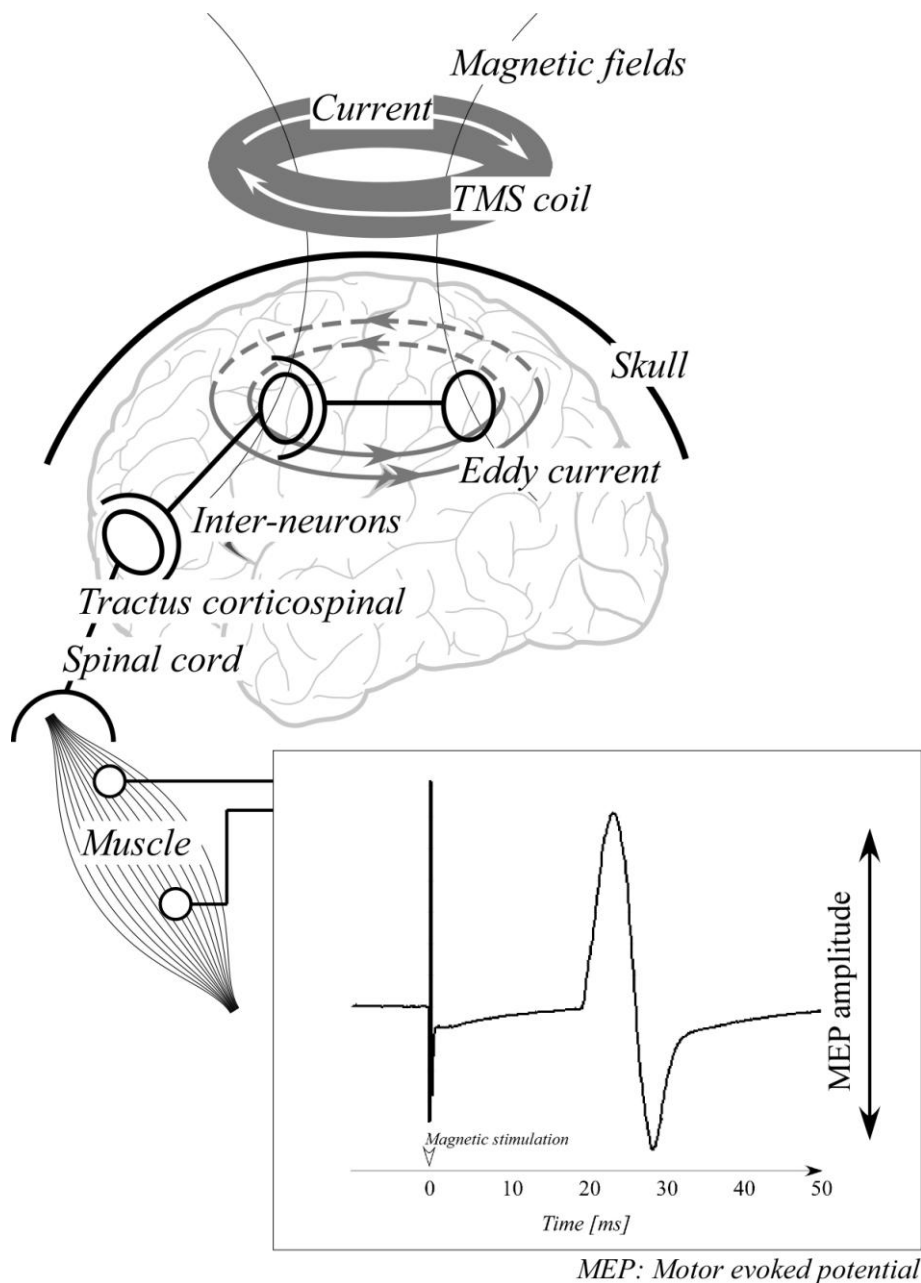
Figure I-4 Mechanism of transcranial magnetic stimulation (Mano et al., 2003).

excitement is transmitted to the cortical spinal cord neurons, which induces the muscle volley. More focused magnetic stimulation was used for the study of the cortical regional map such as for visual perception, memory and muscle control function (Paus et al., 1997; Cohen et al., 1989; Pascual- Leone et al., 1996b).

TMS is a useful and safe tool for the investigation of physiological functions. In addition, it can be safely applied to the diagnosis or treatment of disease (Wassermann, 1998). For example, the modulation of cortical excitability by TMS indicates antidepressant efficacy (Hoflich et al., 1993; George et al., 1997, 1995; Klein et al., 1999). Repetitive TMS (*r*TMS) to the same cortical area is useful in cerebral nerve physiology studies and was introduced in 1987 by Pascual-Leone et al. The prototype of TMS was technically limited, and at the time the largest possible stimulation frequency was 1 Hz. In modern technology, *r*TMS can deliver a series or train of magnetic pulses at a stimulation frequency of 50 Hz or more (Hallett, 1996, 2007). However, high-frequency *r*TMS can induce an epileptic seizure; it is thought that high-frequency *r*TMS increases cortical excitability (Pascual-Leone et al., 1993). In fact, an increase of blood flow and neuronal excitement by *r*TMS are observed in the cortex directly under the magnetic coil (Tergau et al., 1997). These observations suggest that *r*TMS to the cortex may modulate cortical excitability (Maeda et al., 2000; Touge et al., 2001; Wassermann and Lisanby 2001; Ridding and Rothwell 2007; Hallett 2007). Therefore, whether stimulation is at high- or low-frequency is very important. For example, high-frequency *r*TMS may induce an increase in cerebral blood flow and cortical excitability in the region under the magnetic coil. In contrast, low-frequency *r*TMS may induce an opposite effect (Chen et al., 1997; Tergau et al., 1997). However, the mechanism by which *r*TMS alters the excitability of the cortex is not known (Maeda et al., 2000; Touge et al., 2001; Wassermann and Lisanby 2001; Ridding and Rothwell 2007; Hallett 2007). In *r*TMS studies of the incunabulum, noninvasive stimulation of the human brain was used to investigate the effects on the primary motor area, and many studies of the effects of TMS and *r*TMS concentrate on motor evoked potential, which is used to evaluate the effects of magnetic stimulation. A study by Chen et al.

(1997) suggested that low-frequency *r*TMS might decrease the excitability of the motor cortex. Recently, TMS and *r*TMS were applied to an impact statement study of magnetic stimulation, and in particular, electroencephalography (EEG) was used to measure the event-related potentials (ERPs) produced (Pascual-Leone et al., 2000; Hamada et al., 2007; Thickbroom et al., 2006; Iramina et al., 2002; Iramina et al., 2003; Paus et al., 2001; Thut et al., 2005).

The applications of magnetic stimulation extend to the clinical realm. *r*TMS to the motor cortex with optimal intensity and frequency may improve the motor function of a patient with Parkinson's disease (Pascual-Leone et al., 1994a). In addition, stimulation to various other cortical areas has been used to treat stroke, neural pain and so on (Pascual-Leone at el., 1994a; Amassian et al., 1997). In particular, the stimulation frequency of *r*TMS that was used in the treatment of each disease was an important parameter. In addition, the effects of magnetic stimulation continue for a long time after the stimulation has ceased. We can predict that the range of uses of TMS and *r*TMS will only widen increasingly based on these advantages (Ridding and Rothwell, 2007).

1.2   Effects on cortical excitability by frequency of rTMS

In 1998, Wassermann defined *r*TMS at a rate of more than 1 Hz as fast or high-frequency *r*TMS and *r*TMS at a rate of less than 1 Hz as slow or low-frequency *r*TMS (Wassermann, 1998; Rossi et al., 2009). Technically, any magnetic stimulation frequency more than 1 Hz is high-frequency *r*TMS, but in the many previous studies, a frequency range from 5 to 20 Hz has been used for high-frequency *r*TMS. In previous studies using low-frequency *r*TMS, a frequency of 1 Hz is generally applied (Hasey, 2001; Hallett, 2007). In these previous studies, the possibility of modulation of cortical excitability was reported depending on the frequency of *r*TMS. Specifically, low-frequency *r*TMS decreases cortical excitability, while high-frequency *r*TMS increases cortical excitability (Wassermann, 1998; Chen et al., 1997; Berardelli et al., 1998). Other *r*TMS parameters besides the stimulation frequency can induce the alteration of cortical excitability (e.g., stimulation period, stimulation region, stimulation strength and stimulation interval). *r*TMS can modify cortical excitability either in a facilitatory or inhibitory fashion, and it is thought that the modification of this cortical excitability depends on the stimulation parameters (Maeda et al., 2000; Pascual-Leon et al., 1998).

TMS and *r*TMS are used to induce cortical excitability based on the combination of various stimulation parameters (Hallett, 2007). For example, theta burst stimulation (TBS) delivers brief, high frequency *r*TMS at approximately 5 Hz. Facilitatory cortical excitability is induced by intermittent magnetic stimulation, and inhibition is induced by continuous magnetic stimulation (Di Lazzaro et al., 2005; Huang et al., 2005). Similarly, the pairing of stimulation to the cortex and the peripheral nerves is termed paired associative stimulation (PAS); in this case, the facilitation of cortical excitability is

caused by synchronous stimulation, and its inhibition by asynchronous stimulation (Stefan et al., 2000; Wolters et al., 2003). Besides magnetic stimulation, transcranial direct current stimulation (tDCS) can be used to affect cortical excitability. Here, anodal stimulation induces the facilitation of cortical excitability, and cathodal stimulation induces inhibition.

In this manner, various types of stimulation including magnetic stimulation, can induce long-term effects. The long-term effects of *r*TMS are considered to be similar to long-term potentiation (LTP) and long-term depression (LTD). Generally, LTP can be induced by high-frequency magnetic stimulation, and LTD can be induced by low-frequency magnetic stimulation. In a previous report, the duration of the effect on the motor cortex was several tens of minutes (Rossi et al., 2009). However, the duration of the effects of magnetic stimulation on the non-motor cortex is unknown. In addition, the duration of the effects of magnetic stimulation on the P300 ERP component is unknown.

Several studies have suggested the possibility that *r*TMS decreases the β-adrenergic receptor and increases dopamine and serotonin (Zyss et al., 1997; Ben-Shachar et al., 1997). High- or low-frequency *r*TMS may facilitate or inhibit cortical excitability, respectively. It is thought that the modulation of cortical excitability by *r*TMS alters the excitability of the cortical neurons (Touge et al., 2001). In depression treatment, Speer et al. observed an increase in regional cerebral blood flow (rCBF) in the left prefrontal cortex (PFC) after high-frequency *r*TMS at 20 Hz, while a reduction in regional cerebral blood flow was observed after low-frequency *r*TMS at 1 Hz (Speer et al., 2000). In addition, the modulation of cortical excitability by *r*TMS may also be affected by stimulus frequency, stimulus intensity, stimulation region and so on (Wang et al., 1996; Nielsen et al., 1997).

1.3   Previous studies and problematic effects of rTMS on Event-related potentials (ERPs)

The combination of EEG and TMS or *r*TMS is particularly useful for the instantaneous investigation of the alteration of cortical excitability, because the EEG has superior temporal resolution (Kähkönen et al., 2005; Ilmoniemi and Kičić. 2010). ERPs are considered to be the response of the cerebrum in various cognitive functions, such as the cognition of a rare presented target signal in the oddball paradigm (Woods et al., 1987). ERPs consist of N100, P200, N200 and P300 and so on. It is thought that the appearance of the P300 component of ERPs reflects the cognition of the target signal stimulation. The positive P300 wave appears approximately 300 ms after the exhibition of the target signal stimulation. Sutton suggested that the P300 component was related to the cognitive process (Sutton et al, 1965). The P300 component is considered to be an electrical phenomenon based on the cognition process in the nervous system, and it occurs in processing cognition in the cortex. In addition, cognition processing is evaluated by the amplitude and latency of the P300. P300 amplitude is affected by the appearance probability and the importance of the target signal, the degree of difficulty of the task and the motivation of the participant. P300 latency reflects the time necessary for cognitive processing. Therefore, P300 latency is the element that is important for the evaluation of cognitive function (Donchin et al, 1988; Johnson, 1993; Polich and Kok, 1995; Yasukouchi et al., 1995; Kugler et al., 1996; Geisler et al., 1999).

In 2001, Evers used the P300 to evaluate the effects of magnetic stimulation (Evers et al., 2001). The effects were evaluated by measuring ERPs induced by 20 or 1 Hz *r*TMS over the left or right dorsolateral prefrontal cortex (DLPFC). ERPs were elicited by a visual oddball paradigm. A significant decrease in P300 latency was only seen after the 20 Hz *r*TMS to the left dorsolateral prefrontal cortex. By measuring EEG, the authors

suggested the possibility that *r*TMS improved cognitive processing. Moreover, the authors showed that ERPs were helpful in evaluating the effects of TMS and *r*TMS on cognitive processing. This study showed that the left hemisphere might be an important region for ERP generation, more so than the right hemisphere. In this study, 1 Hz *r*TMS had no effect on cognitive processing; however, there have been no studies that have examined the effects of low-frequency *r*TMS in detail.

In 2001, Jing et al. investigated the effects on cognitive processing following 10 Hz *r*TMS to the prefrontal cortex (Jing et al., 2001). The effects of *r*TMS were evaluated using the latency and amplitude of the ERPs induced by an auditory oddball paradigm. This study reported that *r*TMS significantly delayed P300 latency, a result in opposition to the reported effects of *r*TMS on the motor cortex (Pascual-Leone et al., 1994a; Berardelli et al., 1998). However, there were no significant effects on the amplitude of the P300 component. The delay in P300 latency suggests that *r*TMS affects the speed of cognition, but not the motivation of participants to perform well in the task (Geisler et al., 1999; Kugler et al., 1996), and the neuronal activity associated with cognition might be altered by *r*TMS. In this study *r*TMS may have inhibited the neuronal activity. Moreover, this result showed that frontal areas might have an important role in cognitive functioning. However, the effects of low-frequency *r*TMS have not been investigated in detail.

Hansenne et al. investigated the effects of different stimulation periods of low-frequency *r*TMS on the latency of several ERP components, such as N100, P200, N200, and P300 (Hansenne et al., 2004). The authors found that 1 Hz *r*TMS to the left prefrontal cortex induced an increase in P300 latency following stimulation of approximately 15 minutes. However, there were no significant effects on the early ERP components of N100, P200, and N200. This result suggests that the inhibition of cortical excitability induced by *r*TMS had an effect on cognitive processing, but not on automatic processing. However, the effects of low-frequency *r*TMS have not been investigated in detail.

In 2005, Cooper et al. confirmed that *r*TMS over the right dorsolateral prefrontal

cortex did not alter P300 amplitude or latency (Cooper et al., 2008). 1 Hz low-frequency *r*TMS to the right dorsolateral prefrontal cortex was applied at 110% of the resting motor threshold (RMT) for a 15 min stimulation train; however, P300 amplitude and latency did not show significant alteration. These results accord with many studies that used P300 in an impact statement on magnetic stimulation. However, the effects of low-frequency *r*TMS have not been investigated in detail.

Iwahashi et al. investigated the effects of TMS over the left supramarginal gyrus (SMG) (Iwahashi et al., 2009). The intensity of magnetic stimulation was 80% of the participant's motor threshold, and the supramarginal gyrus was stimulated via TMS at 150, 200, and 250 ms after the auditory oddball paradigm. The tone stimulation interval of the oddball paradigm is 2500 ms; therefore, the stimulation frequency of TMS was around 0.4 Hz. The authors evaluated the effects of TMS on the modulation of the P300 latency. After TMS to the left supramarginal gyrus, it was confirmed that the P300 latency was increased. In addition, the authors reconfirmed that left supramarginal gyrus contributed to the generation of the P300 ERP component, which may have been processed around 200 ms after the tone stimulation of the oddball paradigm. However, the right supramarginal gyrus was not examined and thus the effect of low-frequency *r*TMS was not investigated in detail.

In another study, Knoch et al. evaluated the effects of *r*TMS without using ERPs (Knoch et al., 2005). In 2005, Knoch et al. confirmed that *r*TMS modulated cognitive processing differentially depending on stimulation frequency. This study investigated the different effects of magnetic stimulation frequency, such as 1 and 10 Hz *r*TMS to the left or right dorsolateral prefrontal cortex. The magnetic stimulation intensity was above 10% of the resting motor threshold. A 60-pulse magnetic stimulation train was applied with a frequency of 1 Hz. Next, 10 Hz *r*TMS of a total of 300 pulses was applied to the cortex, repeated six times with 5 s stimulation and 5 s rest. The authors suggested that the effect of *r*TMS on the left dorsolateral prefrontal cortex depended on the stimulation frequency. In contrast, the effect of *r*TMS on the right dorsolateral prefrontal cortex did not depend on the stimulation frequency. However, the authors did

not investigate the ERPs. Again, the effect of low-frequency *r*TMS has been not investigated in detail.

Overall, these studies suggest that *r*TMS can modulate the speed of cognitive processing. Most studies on the effects of TMS and *r*TMS have focused on ERPs. ERPs are a useful way to evaluate the effects of *r*TMS and TMS on sensory areas (e.g., auditory or visual). In particular, the P300 component of the ERP can be used to evaluate the influence of magnetic stimulation. Several studies have investigated the effects of *r*TMS on cognitive processing by neurophysiological methods. However, the effects of low-frequency *r*TMS, as outlined above, have not been investigated in detail. Furthermore, little is known about the effects on the P300 latency following low-frequency and short-term magnetic stimulation (e.g., 100 magnetic pulses at 1.00, 0.75, 0.50, or 0.25 Hz) using *r*TMS. Thus, the present study analyzed the effects of *r*TMS at 1.00, 0.75, 0.50, and 0.25 Hz in the left-right supramarginal gyrus and dorsolateral prefrontal cortex, followed by the prolonged effects of *r*TMS stimulation on P300 latency.

1.4   *The purpose of the study*

In past studies, cognitive processing was not affected by *r*TMS to the right hemisphere, while *r*TMS to the left hemisphere did produce effects on cognitive processing. However, previous studies indicated that the effects of magnetic stimulation on the left hemisphere depended on the stimulation parameters. In addition, no alteration of the P300 amplitude was observed, while the P300 latency that can be used to evaluate the effects of *r*TMS or TMS was altered.

Cortical excitability decreased by low-frequency *r*TMS of less than approximately 1 Hz is inhibition, and cortical excitability increased by high-frequency *r*TMS of more than approximately 5 Hz is facilitation (Pascual-Leone et al., 1994a; Chen et al., 1997; Berardelli et al., 1998). These results can be traced to the effects of magnetic stimulation on the motor cortex (Hallett et al., 2000; Cooke et al., 2006). In the many previous studies of previous magnetic stimulation effects, the motor cortex was targeted. As a result, safe guidelines for magnetic stimulation were drawn up. Nevertheless, these guidelines concerning magnetic stimulation's influence on the motor cortex are also applied to non-motor cortical areas. However, how relevant the motor cortex guidelines are to the non-motor cortex is unknown. The study of magnetic stimulation effects on the non-motor cortex has not progressed very far. Therefore, it is thought that magnetic stimulation on the non-motor cortex cannot proceed with complete safety (Rossi et al., 2009) and investigations of the effects on each stimulation region are required. Different stimulation parameters and stimulation of slightly different brain regions may induce reverse or delicately different effects (Pascual-Leone et al., 2000; Jing et al., 2001; Rossi et al., 2009). In fact, the details of the effects of magnetic stimulation on cognitive functioning are unknown.

The aim of this study was to investigate the effects of magnetic stimulation on cognitive processing in detail. In particular, this study focused on the effects of

low-frequency *r*TMS, stimulation effects on the non-motor areas. This study evaluates the effects of magnetic stimulation on the P300 latency of the ERPs. We evaluated the effects of low-frequency (1.00, 0.75, 0.50 or 0.25 Hz) *r*TMS on the supramarginal gyrus and dorsolateral prefrontal cortex, which are considered to be the regions related to P300 origin (Halgren et al., 1998). These results are compared with the results of previous studies on the stimulation of the motor cortex.

*r*TMS with high-frequency or supra-threshold is applied for effects of the magnetic stimulation to the cognitive function. High-frequency *r*TMS has the possibility to elicit epileptic seizures by excessive facilitation of cortical excitability. Moreover, there are few reports using sub-threshold magnetic stimulation. If cortical excitatory facilitation is obtained by low-frequency magnetic stimulation, the facilitation of the excessive cortical excitability may be more reduced than in high-frequency magnetic stimulation. Therefore, the detailed study of *r*TMS with low frequency or sub-threshold is indispensable to investigate effects of the magnetic stimulation to the cognitive function. In the therapeutic application of *r*TMS, low-frequency *r*TMS may thus reduce the epileptic seizure risk, and provide safer applications for medical treatment.

Chapter 2

Effects of stimulation area and frequency on ERP (event-related potential) by before and after rTMS (repetitive transcranial magnetic stimulation)

Reference paper

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- *Frequency Dependence of P300 Latency by Low-Frequency Repetitive Transcranial Magnetic Stimulation, T. Torii, A. Sato, M. Iwahashi, K. Iramina, IEEE Transactions on magnetics, vol. 48, No. 11, pp. 2865-2868, Nov, 2012.*
- *Frequency Dependent Effects of Repetitive Transcranial Magnetic Stimulation on the Human Brain, T. Torii, A. Sato, Y. Nakahara, M. Iwahashi, Y. Itoh and K. Iramina, Neuroreport 23(18), pp.1065-1070, 2012.*

Effects of stimulation area and frequency on ERP by before and after *r*TMS

2.1   Introduction

Transcranial magnetic stimulation (TMS) and repetitive transcranial magnetic stimulation (*r*TMS) have been very important techniques for the noninvasive stimulation of the human brain since 1980 (Pascual-Leone, 1991). Before the development of TMS, transcranial electrical stimulation (TES) was used for the noninvasive stimulation of the brain (Merton and Morton 1980). However, electrical stimulation causes pain and discomfort. Further, magnetic stimulation is not affected by the high impedance of the skull, scalp and hair; this magnetic stimulation can induce an electric current (termed an eddy current) on the cortex of the brain in a relatively painless fashion (Hasey, 2001). For this reason, TMS and *r*TMS have been used in the study of cognitive functions such as memory (Pascual-Leone et al., 1996), vision (Evers al., 2001, Paus et al., 1997), audition (Hansenne et al., 2004, Iwahashi et al., 2008), and muscle activity (Cohen et al., 1989). The combination of magnetic stimulation (TMS or *r*TMS) and functional brain imaging methods, such as positron emission tomography (PET), electroencephalography (EEG) and functional magnetic resonance imaging (*f*MRI) is an effective technique for many cerebral function studies. *f*MRI and PET have a low temporal resolution of more than 100 ms (Ilmoniemi et al., 1997; Nikouline et al., 1999; Schürmann et al., 2001; Tiitinen et al., 1999), and the alteration of cortical excitability over the short time frame induced by *r*TMS cannot be observed using these

techniques. In contrast, the combination of EEG and TMS or *r*TMS is ideal for observing such alterations, because EEG has superior temporal resolution.

Since TMS induces motor evoked potentials (MEPs), these transient electrical signals can be used for the evaluation of the magnetic stimulation effect. However, MEPs are only produced after magnetic stimulation to the motor cortex. Recent studies have applied TMS or *r*TMS in combination with the event-related potential (ERP) component of the EEG (Pascual-Leone et al., 2000; Hamada et al., 2007; Thickbroom et al., 2006; Paus et al., 2001; Thut et al., 2005). ERPs have been used to evaluate the effects of TMS or *r*TMS. EEG is also able to be used for magnetic stimulation studies of audition, vision and so on (Jing et al., 2001; Hansenne et al., 2004, Cooper et al., 2008, Iwahashi et al., 2009).

In many previous magnetic stimulation studies, the motor cortex was the target of the magnetic stimulation and MEPs were used for the evaluation of magnetic stimulation effects. More recently, the target of the magnetic stimulation extended to the non-motor cortical areas. However, in neither of these situations was the effect of the low-frequency magnetic stimulation investigated in detail. Moreover, a different stimulation region and different stimulation parameters may cause varied effects. Therefore, this study clarifies the difference in the magnetic stimulation effects based on stimulation region or stimulation frequency. The stimulation effects on the non-motor cortex were evaluated by measuring the P300 latency of the ERP component. Incidentally, it is thought that the source of the generation of the P300 is the supramarginal gyrus (SMG) and dorsolateral prefrontal cortex (DLPFC). Thus, the present study analyzed the effects of low frequency *r*TMS such as 1.00, 0.75, 0.50 or 0.25 Hz to the left-right supramarginal gyrus and dorsolateral prefrontal cortex.

2.2 Experiment methods

2.2.1 Measurement method of the event-related potentials (ERPs)

Figure II-1 illustrates the measurement system used in this study. The measurement system included a *STIM 2* that was generated by a neurophysiological monitor (Compumedics NeuroScan Ltd., Charlotte, NC, USA) that produced the trigger signal and the stimulation sounds at 1 or 2 kHz. The EEG was measured by *BioAMP*, which
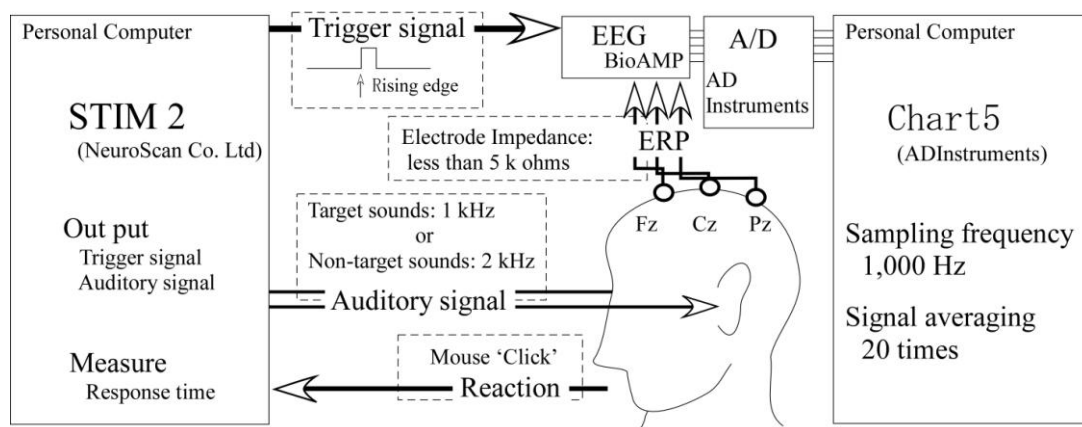

Figure II-1 Measurement system.

The *STIM 2* produces the trigger signal and the 1 kHz or 2 kHz stimulation sounds. Electroencephalography (EEG) data were recorded during the presentation of the target sound.

started the measurement following a trigger signal from *STIM 2*, and a computer was used to record the EEG through an analog-digital convertor (ADInstruments Co. Ltd.).

2.2.2 Condition of auditory oddball task

Figure II-2 illustrates the auditory oddball task used in this study. The auditory oddball task consisted of 1 and 2 kHz sound stimuli. The standard auditory stimulus was a 1 kHz sound (non-target). The deviant auditory stimulus was a 2 kHz sound (target). The standard stimulus was presented on 80% of trials. The deviant stimulus was presented on 20% of trials. The auditory stimuli were randomly presented, consisting of a burst wave with a duration of 50 ms. The interval of the stimulation sounds was 2.5 s,
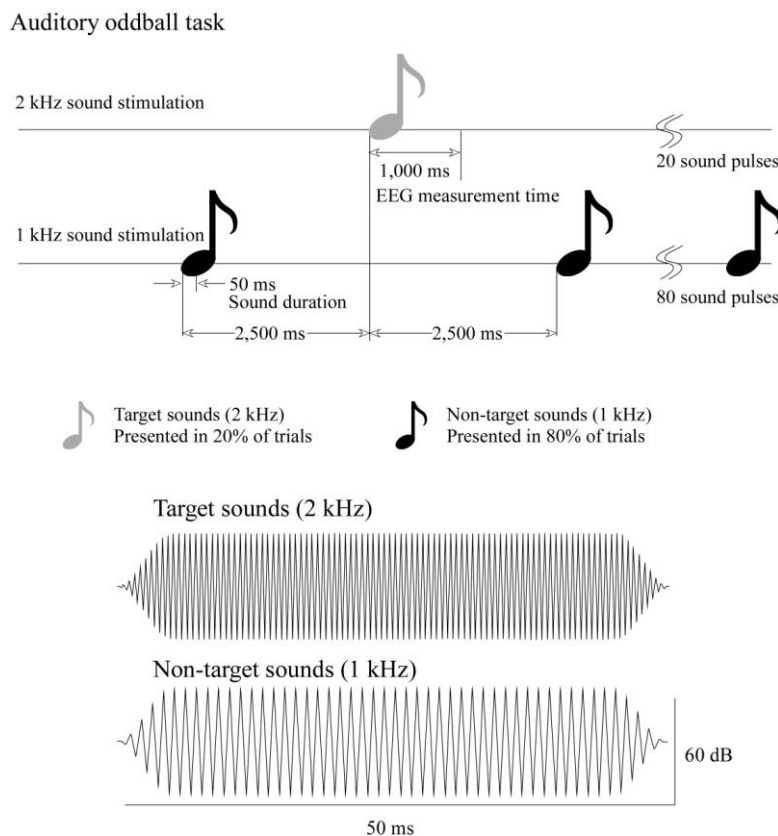
Figure II-2 Auditory oddball task.

and the sound pressure was 60 dB. Stimulus sounds were presented to the participant through earphones.

2.2.3 *Measurement condition of electroencephalography (EEG)*

EEG data were recorded in an electrically shielded room. EEG data were measured at the Fz, Cz, and Pz electrodes according to the international 10–20 system (***Figure II-3 [top]***), and each polar contact impedance was set at less than 5 kΩ. Each EEG recording
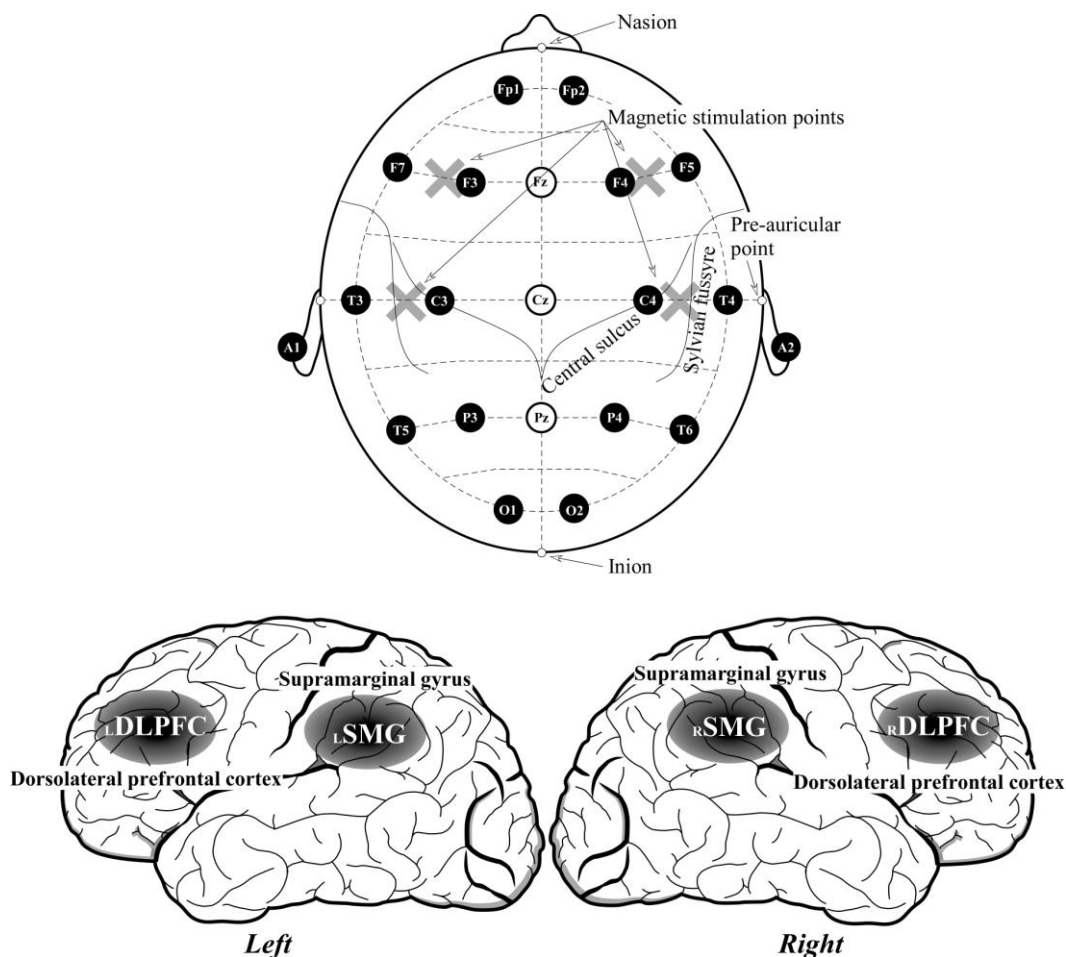
Figure II-3 EEG electrode map and magnetic stimulation points.

period lasted 1.0 s, and recording began with the standing edge of the stimulation sound. The sampling frequency was 1,000 Hz and the synchronized sum (signal averaging) was 20 times. Recorded data were processed using a band-pass digital filter from 0.5 to 50 Hz.

2.2.4 Stimulus condition of repetitive transcranial magnetic stimulation (rTMS)

Figure II-3 (bottom) illustrates the magnetic stimulation areas used in this study. *Figure II-4* illustrates the magnetic stimulation system used in this study. The *Super Rapid Stimulator* (Magstim Co. Ltd.) was used as the magnetic stimulator device, with a flat figure-eight coil (70 mm diameter). *r*TMS was conducted with low frequency magnetic stimulation. The frequency of *r*TMS was 1.00, 0.75, 0.50, and 0.25 Hz, and
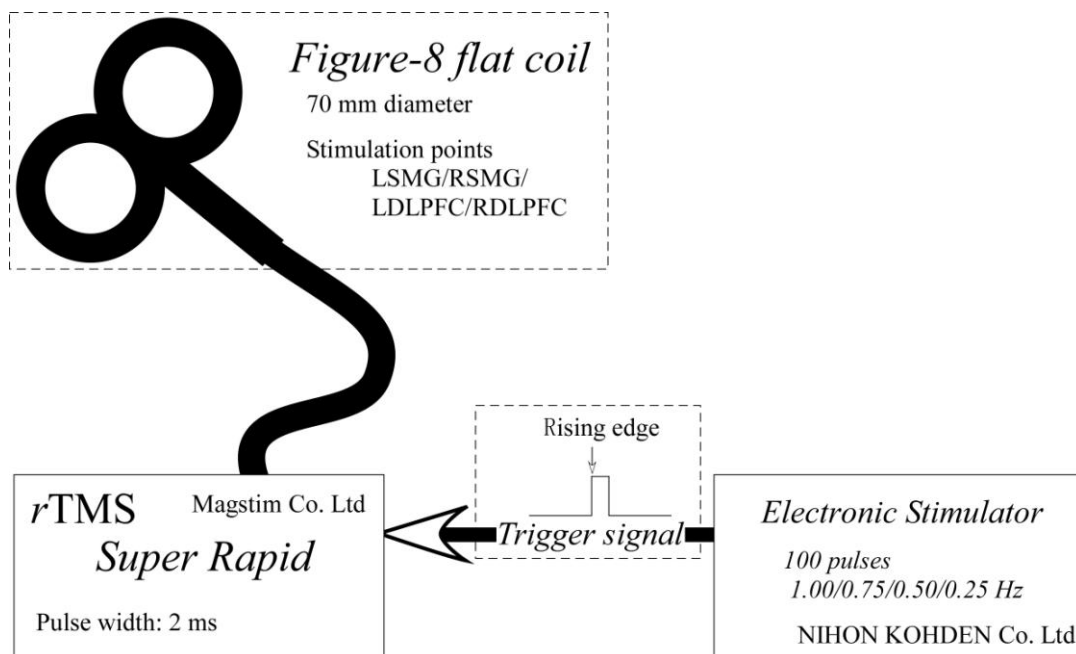
Figure II-4 Magnetic stimulation system.

the stimulation area was the bilateral supramarginal gyrus. The frequency of *r*TMS was 1.00, 0.75, and 0.50 Hz, and the stimulation area was the bilateral dorsolateral prefrontal cortex. *r*TMS was conducted using 100 magnetic pulses with a width of 200 μs. The strength of magnetic stimulation was set at 80% of the participant's motor threshold (MT). The participant's individual motor threshold was the point at which MEPs of more than 50 μV peak-to-peak amplitude were produced in at least five of 10 successive trials (Rossini et al., 1994).

2.2.5 Experimental procedure

Figure II-5 shows the experimental paradigm, which was divided into three phases. In this paradigm, an auditory oddball task was conducted prior to magnetic stimulation as a control condition. *r*TMS was then applied over the left supramarginal gyrus, right

Figure II-5 Experimental paradigm.

The paradigm consisted of conducting the oddball task before and shortly after repetitive transcranial magnetic stimulation (*r*TMS).

supramarginal gyrus, left dorsolateral prefrontal cortex, or right dorsolateral prefrontal cortex. The auditory oddball task was then conducted again immediately following *r*TMS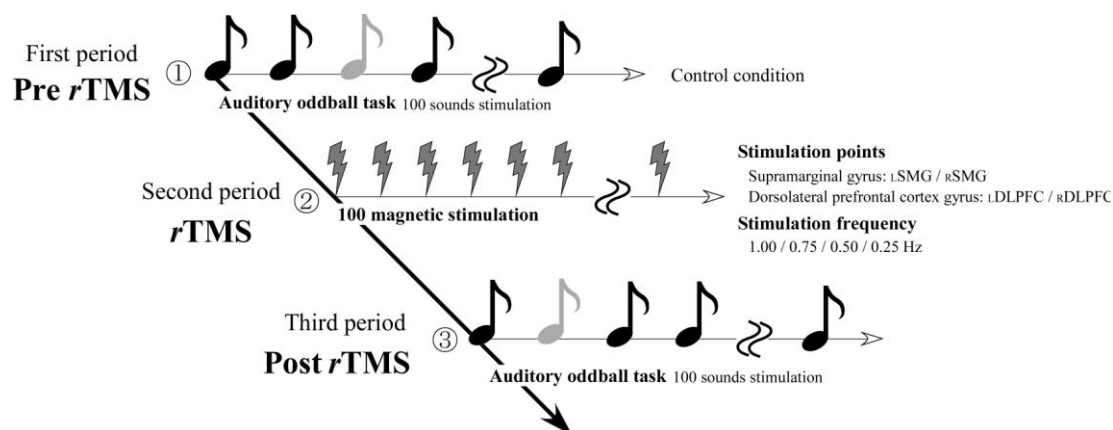 to evaluate the effects of magnetic stimulation. In these studies, the healthy right-handed volunteers were enrolled as participants. Participants' ages ranged from 22 to 57 years of age (***Table II-1***). Total 14 to 17 healthy right-handed volunteers were enrolled in the magnetic stimulation to the supramarginal gyrus. Total 10 healthy right-handed volunteers were enrolled in the magnetic stimulation to the dorsolateral prefrontal cortex, and 4 healthy right-handed volunteers were enrolled in the sham stimulation. Participants were instructed to relax and remain seated during testing. This experiment instructed the participants to click the left mouse button in conjunction with the target sound (the stimulation sound at 2 kHz).

Table II-1 Number of subjects for the experiments by *r*TMS.

	Left supramarginal gyrus	Right supramarginal gyrus	Left dorsolateral prefrontal cortex	Right dorsolateral prefrontal cortex	Sham stimulation
1.00 Hz	14	17	12	10	5
0.75 Hz	15	14	10	10	—
0.50 Hz	14	16	10	10	4
0.25 Hz	14	14	—	—	—

2.3   Results

2.3.1 Effects   of   each   stimulation   frequency   to   left   supramarginal gyrus (SMG)

Figure II-6 shows ERPs at the Cz electrode before and shortly after the magnetic stimulation of 1.00, 0.75, 0.50, and 0.25 Hz over the left supramarginal gyrus. With 1.00 Hz *r*TMS, the P300 latency was reduced shortly after magnetic stimulation compared with the control condition. The P300 latencies decreased by 11.00 ms at the Fz electrode, 9.64 ms at the Cz electrode, and 15.64 ms at the Pz electrode. With 0.75 Hz *r*TMS, the P300 latency was unaltered shortly after magnetic stimulation compared with the control condition. The P300 latencies were only slightly altered by 0.20 ms at the Fz electrode, 2.60 ms at the Cz electrode, and 6.27 ms at the Pz electrode. With 0.50 Hz *r*TMS, the P300 latency expanded shortly after magnetic stimulation compared with the control condition. The P300 latencies increased by 9.00 ms at the Fz electrode, 8.86 ms at the Cz electrode, and 14.29 ms at the Pz electrode. With 0.25 Hz *r*TMS, the P300 latency was unaltered shortly after magnetic stimulation compared with the control condition. The P300 latencies were only slightly altered by 3.50 ms at the Fz electrode, 5.79 ms at the Cz electrode, and 6.43 ms at the Pz electrode.

Paired *t*-test was used to examine for differences of P300 latencies between before and after *r*TMS. *Figure II-7* shows normalized P300 latencies and the ratio of P300 latency before and shortly after magnetic stimulation of the left supramarginal gyrus with 1.00, 0.75, 0.50, and 0.25 Hz *r*TMS. With 1.00 Hz *r*TMS, there was a significant difference on P300 latencies of before and shortly after magnetic stimulation (Fz: $p<0.01$, Cz: $p<0.05$, Pz: $p<0.05$). With 0.75 Hz *r*TMS, there was no difference on P300

latencies of before and shortly after magnetic stimulation. With 0.50 Hz *r*TMS, there was a significant difference on P300 latencies of before and shortly after magnetic stimulation (Fz: $p<0.05$, Cz: $p<0.05$, Pz: $p<0.05$). With 0.25 Hz *r*TMS there was no difference on P300 latencies of before and shortly after magnetic stimulation.

Figure II-6 ERPs at the Cz electrode before and shortly after magnetic stimulation over the left SMG at 1.00, 0.75, 0.50 and 0.25 Hz.

The gray line represents an ERP before the magnetic stimulation, and the black line represents an ERP after the magnetic stimulation.

Figure II-7 Normalized P300 latencies and difference in normalized P300 latencies to each pre-*r*TMS over the left SMG at 1.00, 0.75, 0.50 and 0.25 Hz.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

2.3.2 Effects of each stimulation frequency to right supramarginal gyrus (SMG)

Figure II-8 shows ERPs at the Cz electrode before and shortly after the magnetic stimulation of 1.00, 0.75, 0.50, and 0.25 Hz over the right supramarginal gyrus. With 1.00, 0.75, 0.50, and 0.25 Hz *r*TMS, the P300 latency was unaltered shortly after magnetic stimulation compared with the control condition. With the 1.00 Hz stimulation, the latencies slightly changed by 0.76 ms at the Fz electrode, 2.29 ms at the Cz

rTMS over the right supramarginal gyrus(RSMG)

1.00 Hz rTMS

0.75 Hz rTMS

0.50 Hz rTMS

0.25 Hz rTMS

Target sounds stimulation   5 μV

500
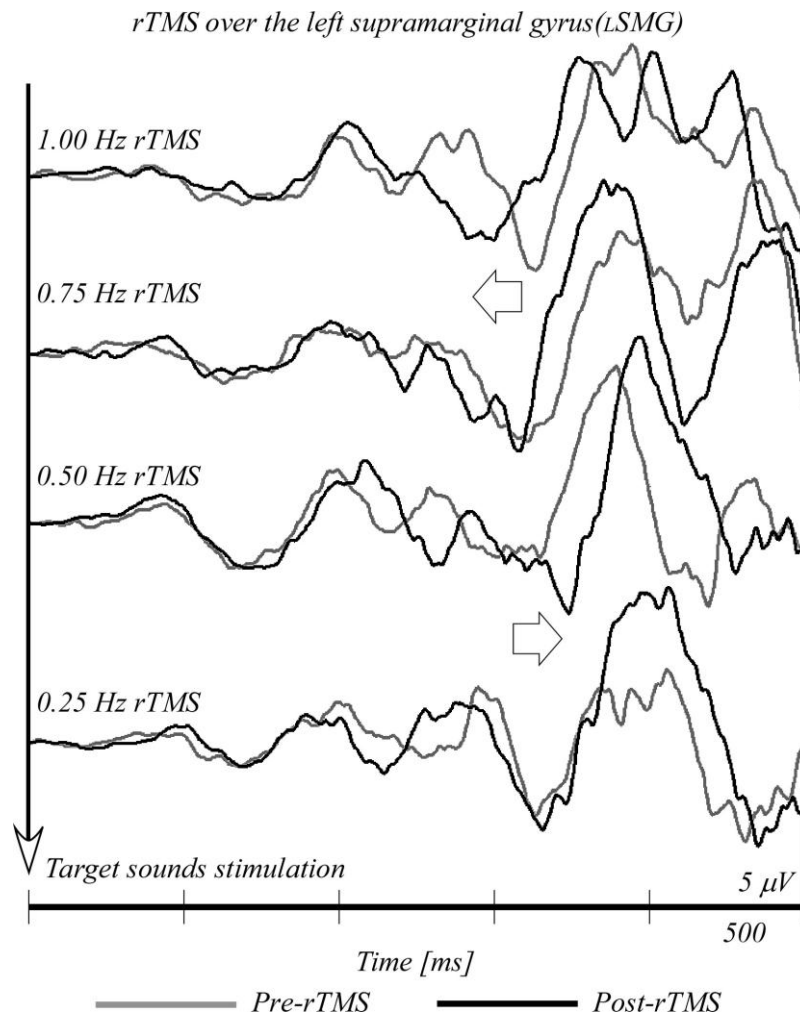
Time [ms]

Pre-rTMS   Post-rTMS

Figure II-8 ERPs at the Cz electrode before and shortly after magnetic stimulation over the right SMG at 1.00, 0.75, 0.50 and 0.25 Hz.

The gray line represents an ERP before the magnetic stimulation, and the black line represents an ERP after the magnetic stimulation.

electrode, and 0.47 ms at the Pz electrode. With 0.75 Hz stimulation, the latencies slightly changed by 3.86 ms at the Fz electrode, 0.71 ms at the Cz electrode, and 2.71 ms at the Pz electrode. With 0.50 Hz stimulation, the latencies slightly changed by 4.19 ms at the Fz electrode, 6.38 ms at the Cz electrode, and 3.00 ms at the Pz electrode. With 0.25 Hz stimulation, the latencies slightly changed by 0.36 ms at the Fz electrode, 5.07 ms at the Cz electrode, and 0.71 ms at the Pz electrode.

Paired *t*-test was used to examine for differences of P300 latencies between before and after *r*TMS. ***Figure II-9*** shows normalized P300 latencies and the ratio of P300
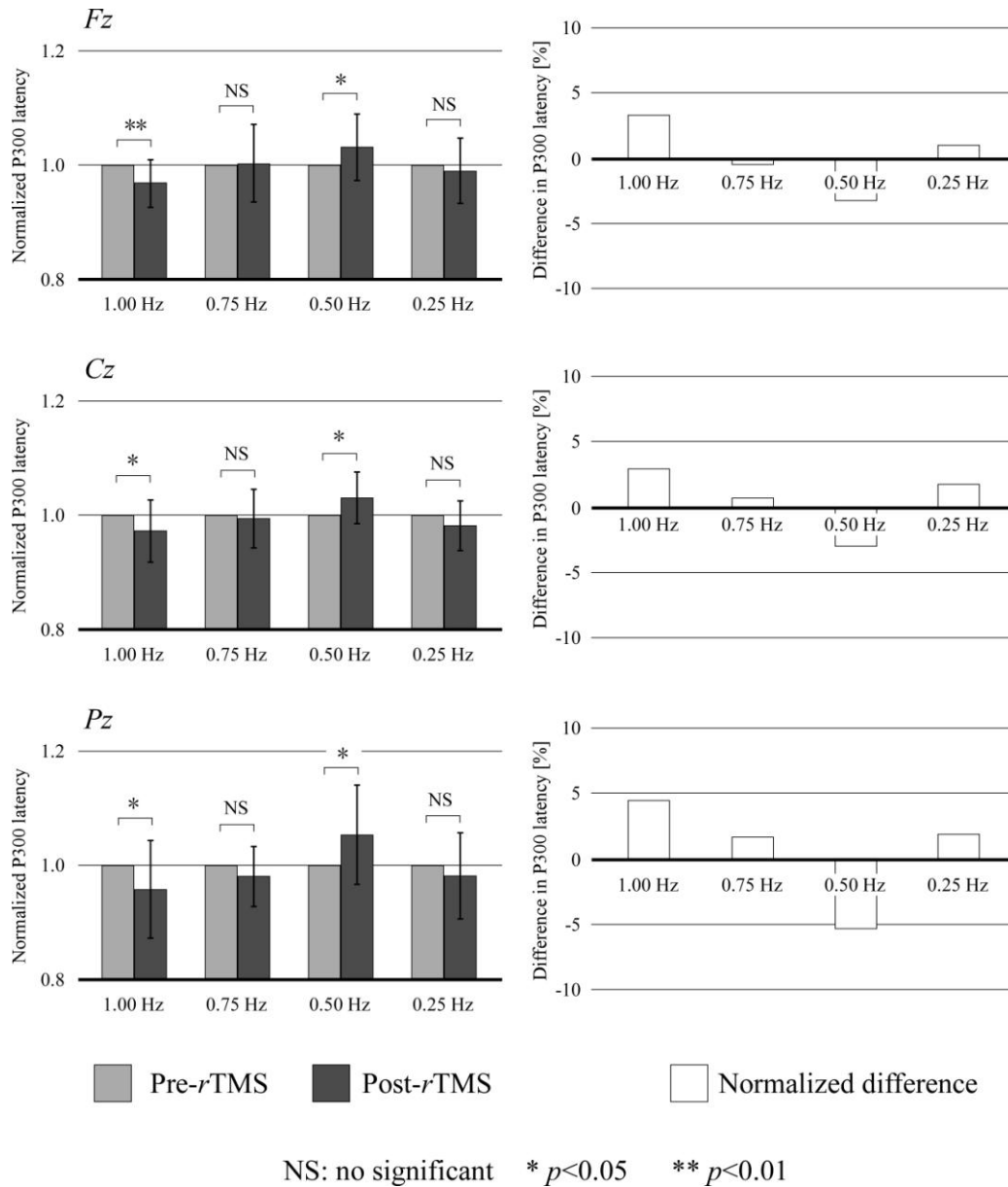

Figure II-9 Normalized P300 latencies and difference in normalized P300 latencies to each pre-*r*TMS over the right SMG at 1.00, 0.75, 0.50 and 0.25 Hz.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

latency before and shortly after magnetic stimulation of the right supramarginal gyrus with 1.00, 0.75, 0.50, and 0.25 Hz *r*TMS. There were no differences on P300 latencies of before and shortly after magnetic stimulation for this area.

2.3.3 *Effects of each stimulation frequency to left dorsolateral prefrontal cortex (DLPFC)*

Figure II-10 shows ERPs at the Cz electrode before and shortly after the magnetic stimulation of 1.00, 0.75, and 0.50 Hz over the left dorsolateral prefrontal cortex. With
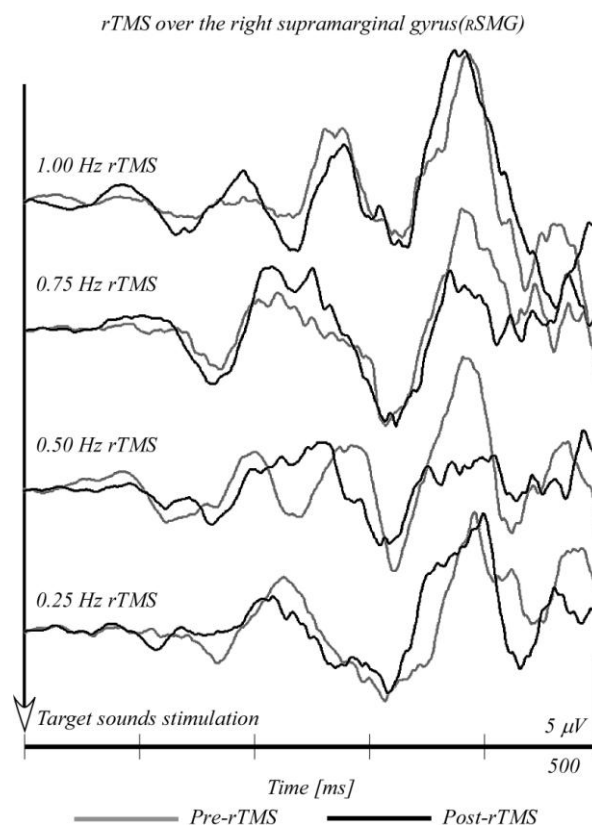

Figure II-10 ERPs at the Cz electrode before and shortly after magnetic stimulation over the left DLPFC at 1.00, 0.75 and 0.50 Hz.

The gray line represents an ERP before the magnetic stimulation, and the black line represents an ERP after the magnetic stimulation.

1.00 Hz *r*TMS, the P300 latency expanded shortly after magnetic stimulation compared with the control condition. The P300 latencies increased by 15.92 ms at the Fz electrode, 18.00 ms at the Cz electrode, and 18.92 ms at the Pz electrode. With 0.75 Hz stimulation the latencies slightly changed by 1.40 ms at the Fz electrode, 0.00 ms at the Cz electrode, and 1.70 ms at the Pz electrode. With 0.50 Hz stimulation, the latencies slightly changed by 3.40 ms at the Fz electrode, 5.40 ms at the Cz electrode, and 4.00 ms at the Pz electrode.

Paired *t*-test was used to examine for differences of P300 latencies between before and after *r*TMS. ***Figure II-11*** shows normalized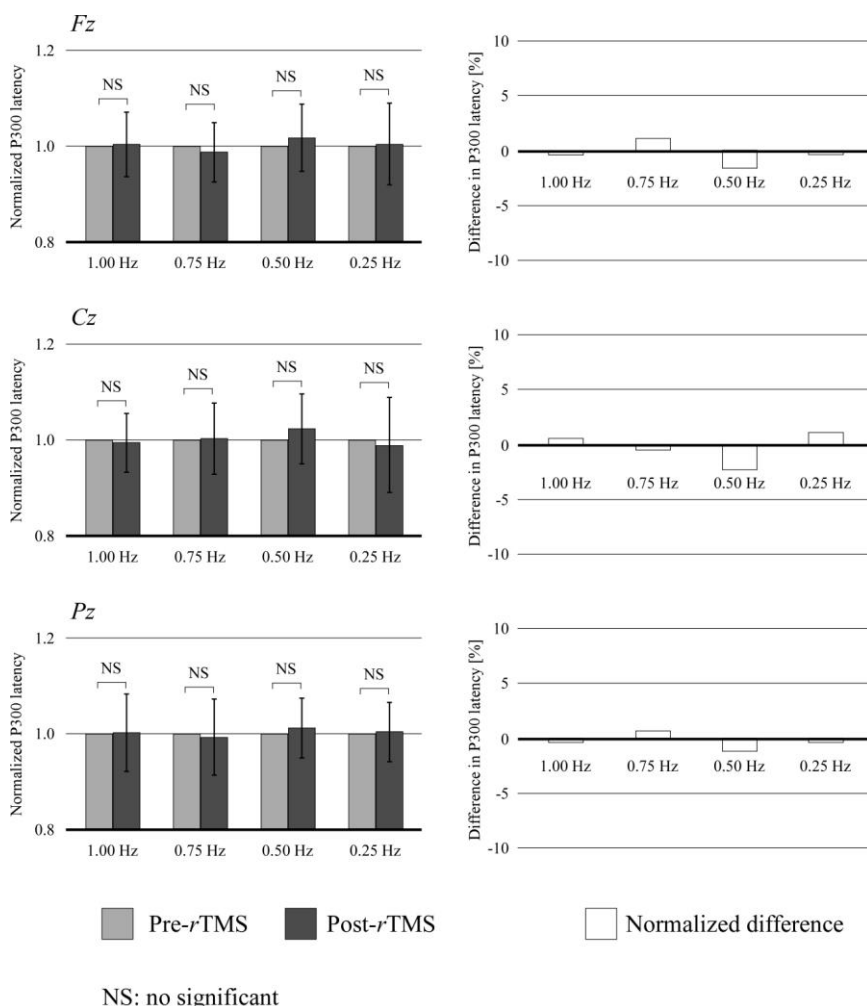 P300 latencies and the ratio of P300 latency before and shortly after magnetic stimulation of the left dorsolateral prefrontal cortex with 1.00, 0.75, and 0.50 Hz *r*TMS. With 1.00 Hz *r*TMS, there was a significant difference on P300 latencies of before and shortly after magnetic stimulation (Fz: $p<0.05$, Cz: $p<0.05$, Pz: $p<0.05$). With 0.75 and 0.50 Hz *r*TMS, there was no difference on P300 latencies of before and shortly after magnetic stimulation..

Figure II-11 Normalized P300 latencies and difference in normalized P300 latencies to each pre-*r*TMS over the left DLPFC at 1.00, 0.75 and 0.50 Hz.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

2.3.4 *Effects of each stimulation frequency to right dorsolateral prefrontal cortex (DLPFC)*

Figure II-12 shows ERPs at the Cz electrode before and shortly after the magnetic stimulation of 1.00, 0.75, and 0.50 Hz over t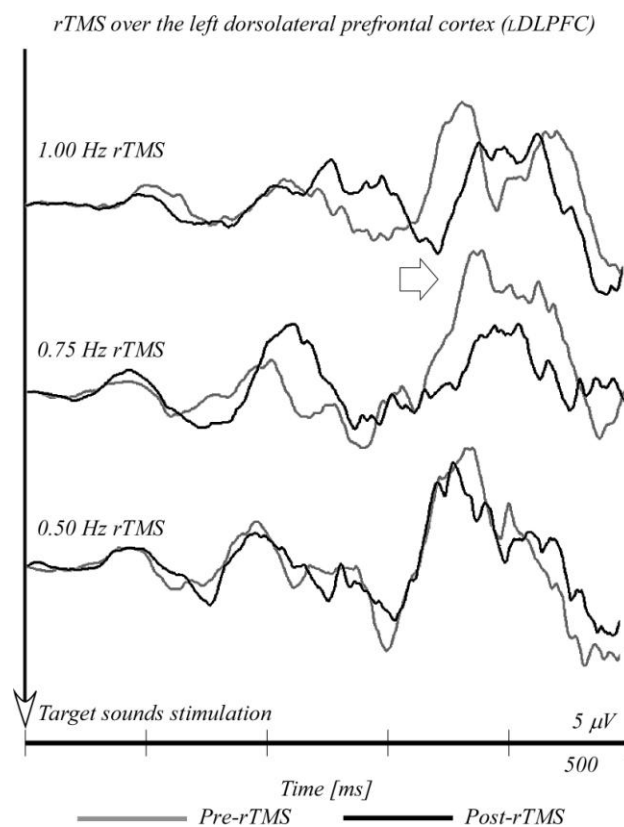he 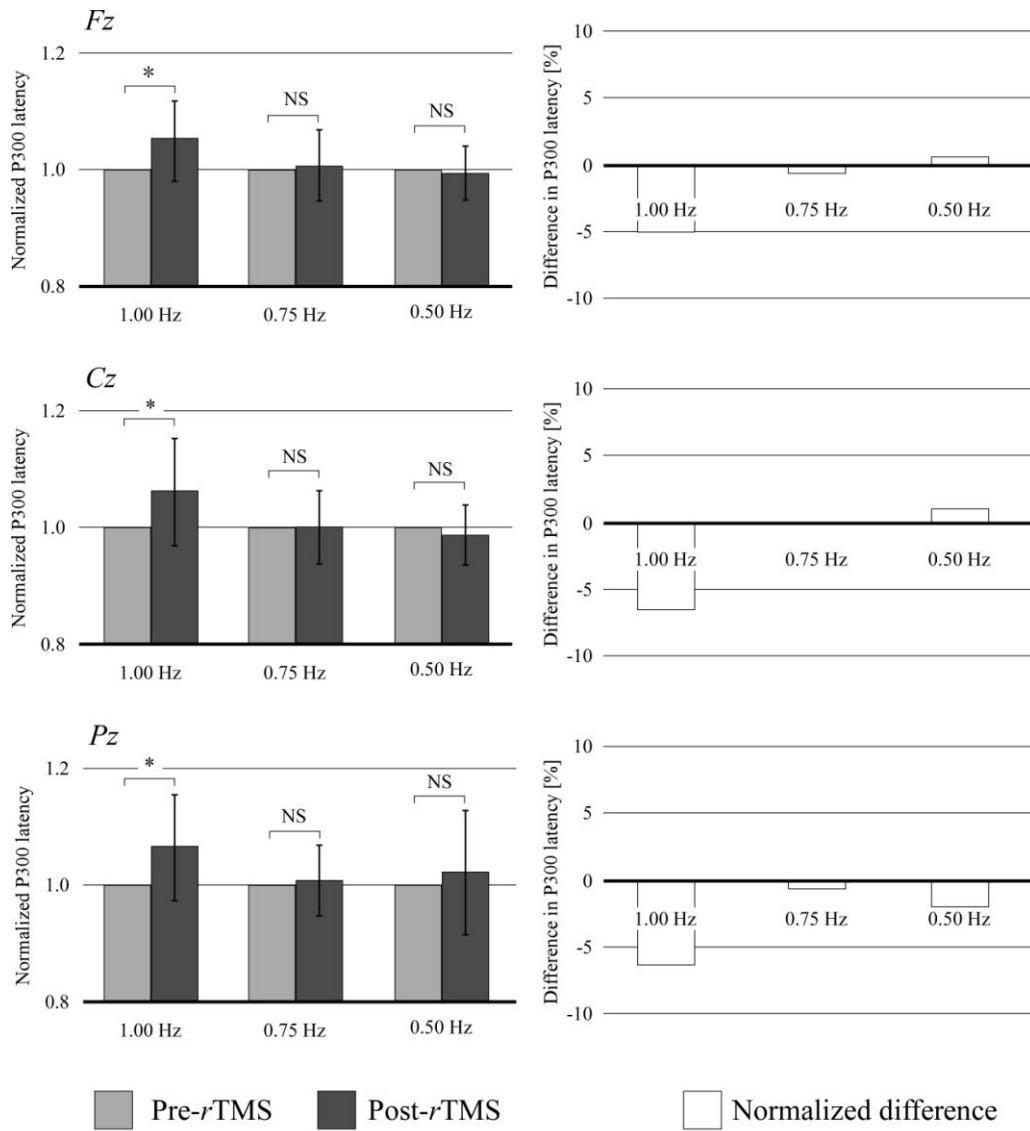right dorsolateral prefrontal cortex. With 1.00, 0.75, and 0.50 Hz *r*TMS, the P300 latency was unaltered shortly after magnetic stimulation compared with the control condition. With the 1.00 Hz stimulation, the latencies slightly changed by 0.40 ms at the Fz electrode, 4.80 ms at the Cz electrode,

Figure II-12 ERPs at the Cz electrode before and shortly after magnetic stimulation over the right DLPFC at 1.00, 0.75 and 0.50 Hz.

The gray line represents an ERP before the magnetic stimulation, and the black line represents an ERP after the magnetic stimulation.

and 6.70 ms at the Pz electrode. With 0.75 Hz stimulation, the latencies slightly changed by 3.10 ms at the Fz electrode, 2.40 ms at the Cz electrode, and 0.20 ms at the Pz electrode. With 0.50 Hz stimulation, the latencies slightly changed by 3.70 ms at the Fz electrode, 4.60 ms at the Cz electrode, and 2.50 ms at the Pz electrode.

Paired *t*-test was used to examine for differences of P300 latencies between before and after *r*TMS. ***Figure II-13*** shows normalized P300 latencies and the ratio of P300 latency before and shortly after magnetic stimulation of the right dorsolateral prefrontal
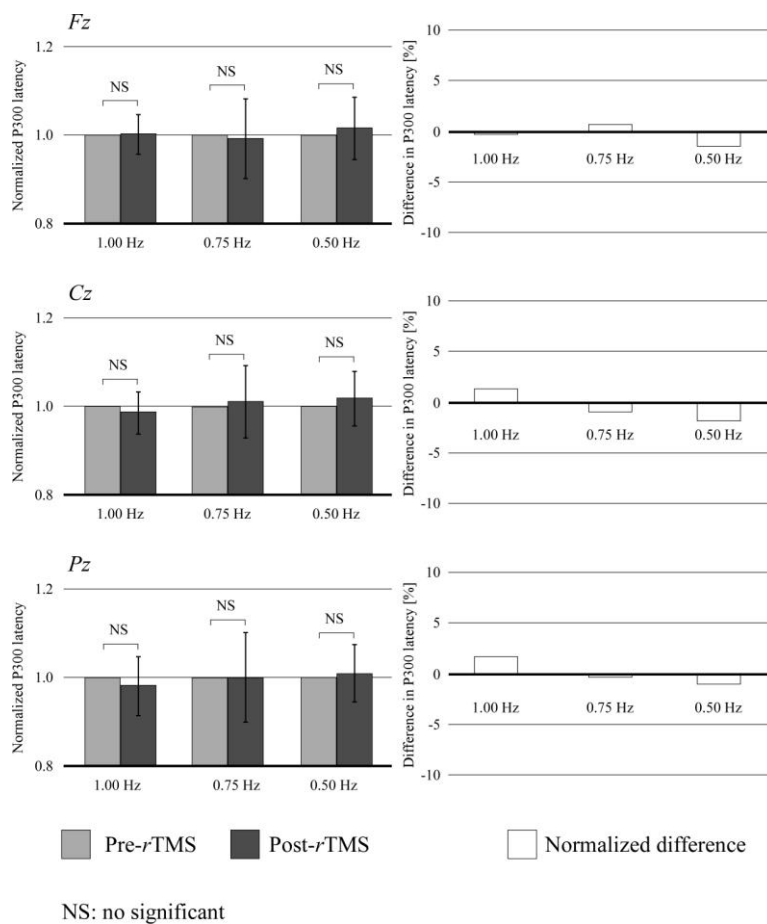
Figure II-13 Normalized P300 latencies and difference in normalized P300 latencies to each pre-*r*TMS over the right DLPFC at 1.00, 0.75 and 0.50 Hz.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

cortex with 1.00, 0.75, and 0.50 Hz *r*TMS. There were no differences on P300 latencies of before and shortly after magnetic stimulation for this area.

2.3.5 Verification by the sham stimulation

Figure II-14 shows ERPs at the Cz electrode before and shortly after the sham magnetic stimulation of 1.00 and 0.50 Hz. With 1.00 and 0.50 Hz *r*TMS, the P300 latency was unaltered shortly after the sham magnetic stimulation compared with the
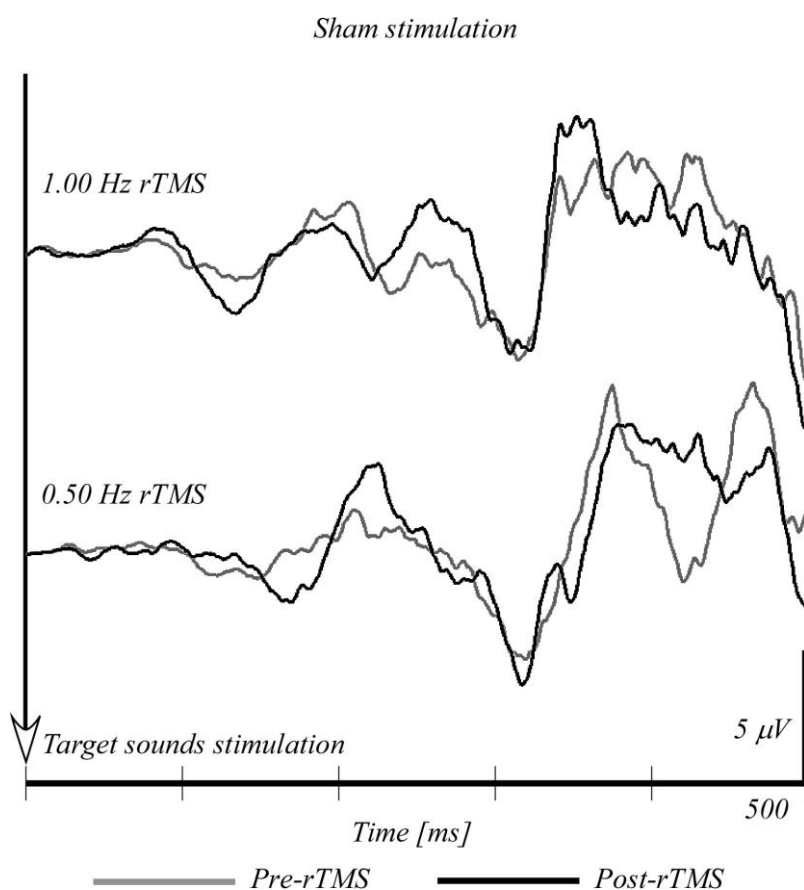
Figure II-14 ERPs at the Cz electrode before and shortly after sham magnetic stimulation at 1.00 and 0.50 Hz.

The gray line represents an ERP before the magnetic stimulation, and the black line represents an ERP after the magnetic stimulation.

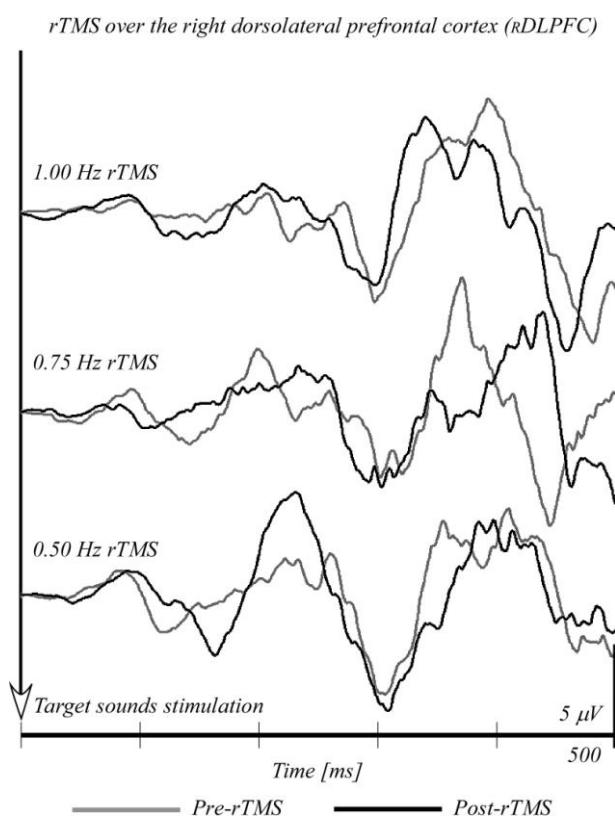control condition. With the 1.00 Hz stimulation, the latencies slightly changed by 2.00 ms at the Fz electrode, 0.00 ms at the Cz electrode, and 2.20 ms at the Pz electrode. With 0.50 Hz stimulation, the latencies slightly changed by 2.25 ms at the Fz electrode, 4.25 ms at the Cz electrode, and 6.25 ms at the Pz electrode.

Paired *t*-test was used to examine for differences of P300 latencies between before and after *r*TMS. ***Figure II-15*** shows normalized P300 latencies and the ratio of P300
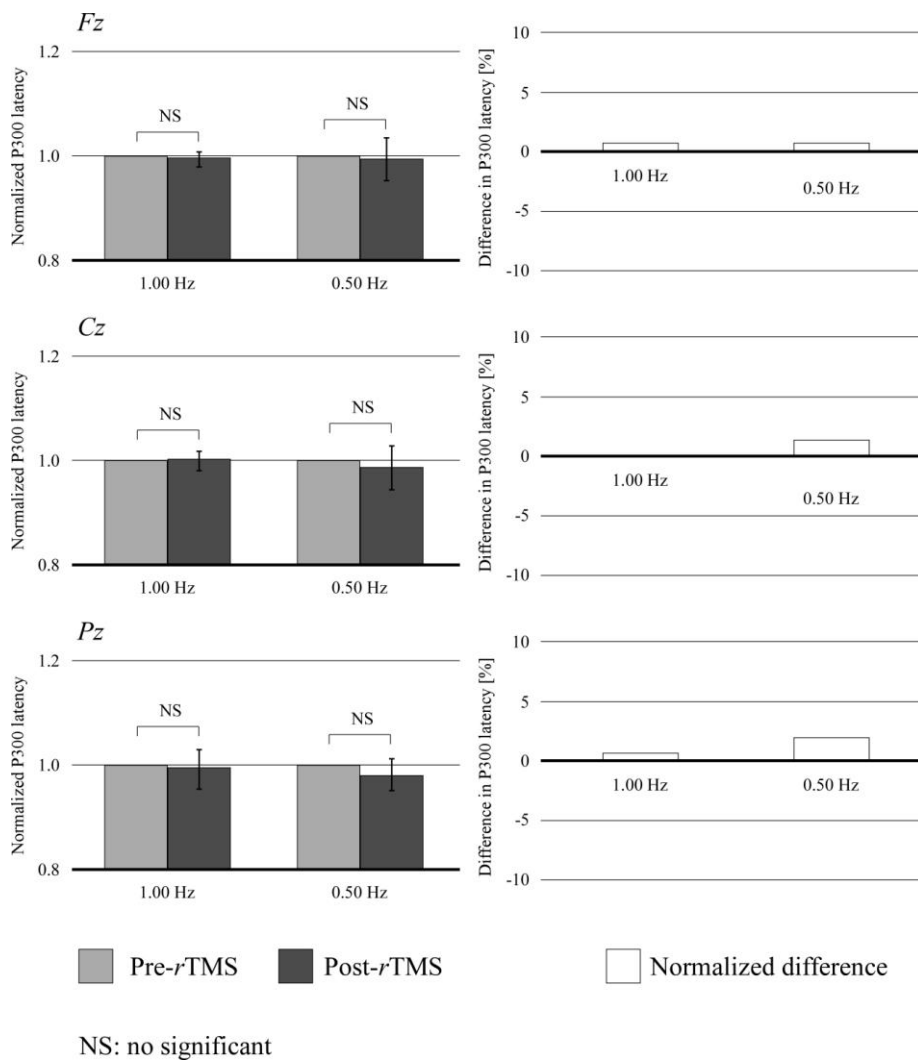
Figure II-15 Normalized P300 latencies and difference in normalized P300 latencies to each pre-*r*TMS sham *r*TMS at 1.00 and 0.50 Hz.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

latency before and shortly after sham magnetic stimulation with 1.00 and 0.50 Hz *r*TMS. There were no differences on P300 latencies of before and shortly after sham magnetic stimulation.

2.4   Discussion

*r*TMS may affect excitatory neurons, and it is thought that *r*TMS induces modulation of cortical excitability (Mano et al., 1993a; Mano et al., 1993b). The results of this study provide support for the concept that low frequency magnetic stimulation modulates the cognitive function. The facilitation or inhibition of the cortex excitability in association with the cognitive function may be affected by magnetic stimulation. It is generally thought that an increase (facilitation) in cortical excitability is induced by high-frequency *r*TMS, whereas a decrease (inhibition) in cortical excitability is induced by low-frequency *r*TMS (Wassermann, 1998; Chen et al., 1997; Berardelli et al., 1998, Hallett, 2000). Therefore, in this study, it was hypothesized that low-frequency (1.00, 0.75, 0.50, or 0.25 Hz) *r*TMS would lead to a delay in P300 latencies. This hypothesis was supported by the effect of 1.00 Hz *r*TMS over the left dorsolateral prefrontal cortex and 0.50 Hz *r*TMS over the left supramarginal gyrus. However, the observed increase in latency was not obtained after low-frequency magnetic stimulation at 1.00, 0.75, or 0.25 Hz over the left supramarginal gyrus and 0.75 or 0.50 Hz *r*TMS over the left dorsolateral prefrontal cortex, or after low-frequency magnetic stimulation over the right supramarginal gyrus and dorsolateral prefrontal cortex.

FigureII-16 shows magnetic stimulation frequency and the relation of the effect in each stimulation region. The reduction of the P300 latency was produced by consecutive pulses of 1.00 Hz *r*TMS to the left supramarginal gyrus. These results suggested that 1.00 Hz *r*TMS to the left supramarginal gyrus facilitated cortical excitability, while 0.50 Hz *r*TMS to the left supramarginal gyrus inhibited cortical excitability. *r*TMS (1.00, 0.75, 0.50, and 0.25 Hz) to the right supramarginal gyrus or dorsolateral prefrontal cortex, *r*TMS (0.75 and 0.25 Hz) to the left supramarginal gyrus and *r*TMS (0.75, and 0.50 Hz) to the left dorsolateral prefrontal cortex were not obtained the modulation on the P300 latency. Incidentally, the supramarginal gyrus and

dorsolateral prefrontal cortex may be regions contributing to the generation of the P300 component (Halgren et al., 1998). However, the P300 latency in the right supramarginal gyrus and dorsolateral prefrontal cortex was minimally altered compared with the left supramarginal gyrus and dorsolateral prefrontal cortex. These results suggest that the left supramarginal gyrus exhibits the greatest susceptibility to magnetic stimulation and contributes to the highest generation of the P300 component when compared with other areas. Indeed, the results of the present study show no significant alterations in P300 latency, regardless of magnetic stimulation frequency, over the right supramarginal gyrus and dorsolateral prefrontal cortex. These results are consistent with other frequency-dependent effects observed in the left, but not the right, dorsolateral prefrontal cortex (Knoch et al., 2005), indicating that low-frequency _r_TMS applied to the right dorsolateral prefrontal cortex would produce no significant changes in P300 latency (Cooper et al., 2008).

In conclusion, the aim of this study was to clarify the effects of low-frequency _r_TMS on human brain activity. The P300 latency of ERPs was used to evaluate the effects of

Left dorsolateral prefrontal cortex

1.00 Hz : P300 latency	Delay	
0.75 Hz : P300 latency	No change	
0.50 Hz : P300 latency	No change	

Right dorsolateral prefrontal cortex

1.00 Hz : P300 latency	No change
0.75 Hz : P300 latency	No change
0.50 Hz : P300 latency	No change

Left supramarginal gyrus

1.00 Hz : P300 latency	Shortened
0.75 Hz : P300 latency	No change
0.50 Hz : P300 latency	Delay
0.25 Hz : P300 latency	No change

Right supramarginal gyrus

1.00 Hz : P300 latency	No change
0.75 Hz : P300 latency	No change
0.50 Hz : P300 latency	No change
0.25 Hz : P300 latency	No change

Figure II-16 The relations of magnetic stimulation frequency and the effects.

low-frequency *r*TMS by stimulating the bilateral supramarginal gyrus and dorsolateral prefrontal cortex. *r*TMS at 1.00, 0.75, 0.50, and 0.25 Hz were used as low-frequency magnetic stimulation intensities, although significant effects were only observed after magnetic stimulation at 1.00 and 0.50 Hz over the left supramarginal gyrus, and 0.50 Hz *r*TMS over the left dorsolateral prefrontal cortex. Stimulation of the left supramarginal gyrus at 1.00 and 0.50 Hz produced the opposite effects on P300 latency. Stimulation of the left dorsolateral prefrontal cortex at 1.00 and 0.75 or 0.50 Hz produced different effects on P300 latency. Thus, the effects of *r*TMS to the left supramarginal gyrus and dorsolateral prefrontal cortex on P300 latencies are frequency dependent. By contrast, *r*TMS over the right supramarginal gyrus and dorsolateral prefrontal cortex had no significant effect on P300 latencies, and is therefore not frequency dependent.

Based on the results of this study, it is thought that the supramarginal gyrus and dorsolateral prefrontal cortex in the left hemisphere are associated with the generation of the P300 component, and it is speculated that the left hemisphere strongly participates in the generation of the P300 component compared with the supramarginal gyrus and dorsolateral prefrontal cortex in the right hemisphere.

2.5   Summary

The aim of this study was to investigate the effects of repetitive transcranial magnetic stimulation (*r*TMS) on brain activity. The latency of the P300 component of the event-related potentials (ERPs) was used to evaluate the effects of low-frequency and short-term *r*TMS over the areas thought to be related to the generation of the P300, including the supramarginal gyrus and dorsolateral prefrontal cortex. A flat figure-eight coil was used to stimulate the left and right supramarginal gyrus and dorsolateral prefrontal cortex, with magnetic stimulation applied at an intensity that was 80% of the participant's motor threshold. A total of 100 magnetic pulses were applied in *r*TMS, with stimulation frequencies of 1.00, 0.75, 0.50, or 0.25 Hz. ERPs were measured while participants completed the oddball task before and after *r*TMS. The oddball task was performed shortly after *r*TMS, and ERP was then measured to evaluate P300 latency. As a control condition, ERPs were measured before *r*TMS. EEG was measured at Fz, Cz, and Pz of the international 10–20 electrode system.

With 1.00 Hz low-frequency magnetic stimulation over the left supramarginal gyrus, P300 latency was reduced. Compared with the P300 latency of before *r*TMS, the latency differed by approximately 14 ms at the Fz electrode. By contrast, P300 latency increased after 0.50 Hz *r*TMS. Compared with the P300 latency before *r*TMS, the latency was increased by approximately 10 ms at the Fz electrode. However, at 0.75 and 0.25 Hz *r*TMS, no change in P300 latencies was observed after *r*TMS. With 1.00 Hz low-frequency magnetic stimulation over the left dorsolateral prefrontal cortex, P300 latency was increased. Compared with the P300 latency before *r*TMS, the latency was increased by approximately 18 ms at the Fz electrode. However, at 0.75 and 0.50 Hz *r*TMS, no changes in P300 latencies were observed after *r*TMS. With magnetic stimulation over the right supramarginal gyrus and dorsolateral prefrontal cortex, no changes in P300 latencies were observed after *r*TMS. These different effects on P300

latency occurred between 1.00, 0.75, 0.50, or 0.25 Hz *r*TMS, and the left-right hemisphere and supramarginal gyrus-dorsolateral prefrontal cortex.

Chapter 3

Verification experiments

Verification experiments

3.1 The magnetic stimulation effect at 120% of the motor threshold

3.1.1 Introduction

This study observed the increase of cortex excitability by the low frequency *r*TMS with sub-threshold. Lang et al. (2006) also observed increase of cortex excitability by the low frequency *r*TMS with sub-threshold. In contrast, the cortex excitability was decreased by the low frequency *r*TMS to motor cortex with supra-threshold. Therefore, in this chapter, the experiment by the low frequency *r*TMS with supra-threshold was tried.

3.1.2 Experiment condition

The method of experiment follows Chapter2. However, the stimulation parameters of *r*TMS were as follows. The magnetic stimulation was 1 Hz *r*TMS to the left supramarginal gyrus; see ***Figure II-3 (bottom)***. The stimulus intensity was 120% of a

participant's motor threshold (Rossini et al., 1994). In this study, 10 healthy right-handed volunteers were enrolled as participants. Participants' ages ranged from 22 to 40 years.

3.1.3 Results

Figure IV-1 shows ERPs at the Cz electrode before and after the magnetic stimulation of 1 Hz *r*TMS at 80 and 120% of the motor threshold for the left supramarginal gyrus. For *r*TMS at 80% of the motor threshold, the P300 latency was reduced immediately after magnetic stimulation compared with the control condition. In
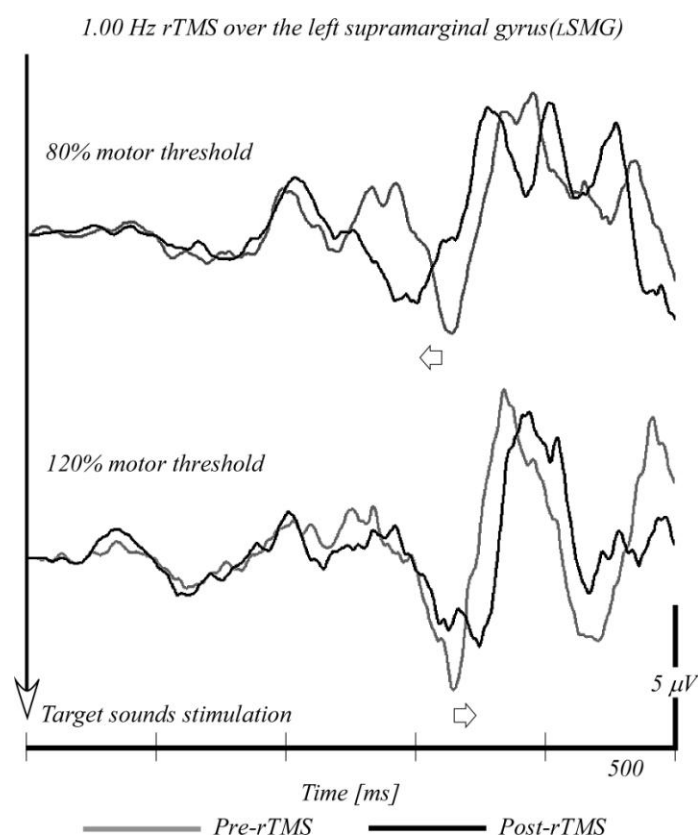
Figure Ⅳ-1 ERPs at the Cz electrode before and after 1.00 Hz *r*TMS at 80% or 120% of the motor threshold over the left SMG.

contrast, with *r*TMS at 120% of the motor threshold, the P300 latency was increased immediately after magnetic stimulation compared with the control condition. The P300 latencies were increased by 10.40 ms at the Fz electrode, 9.80 ms at the Cz electrode, and 12.30 ms at the Pz electrode.

Figure IV-2 shows normalized P300 latencies and the ratio of P300 latency before and shortly after magnetic stimulation of the left supramarginal gyrus with 1.00 Hz *r*TMS at 120% of the motor threshold. For 1.00 Hz *r*TMS at 80% of the motor threshold, P300 latency was shortened by magnetic stimulation (see Chapter 2). With 1.00 Hz *r*TMS at 120% of the motor threshold, there was a significant difference before and immediately after *r*TMS (Fz: $p < 0.05$, Cz: $p < 0.05$, Pz: $p < 0.05$).
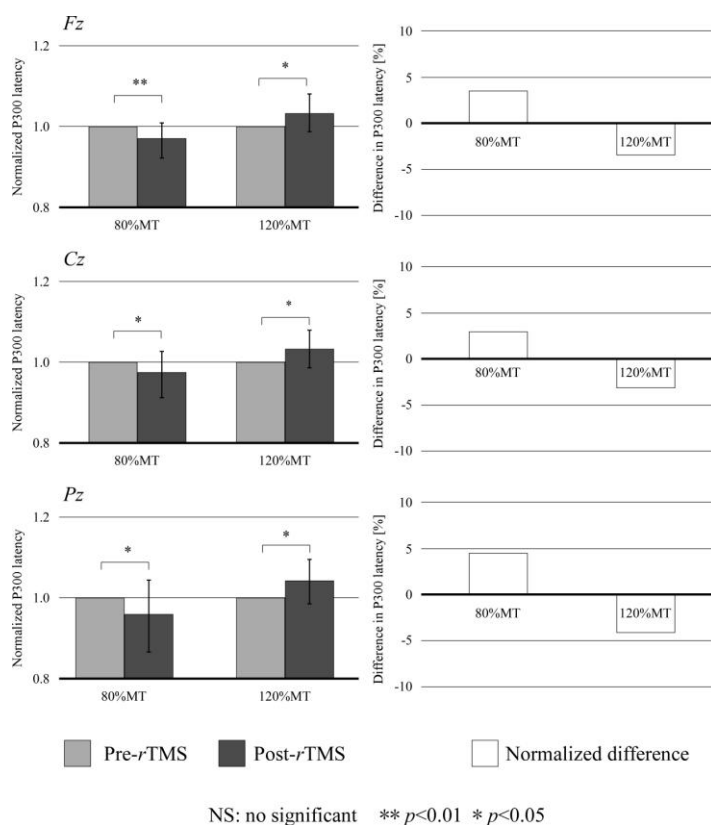
Figure Ⅳ-2 Normalized P300 latencies and difference in normalized P300 latencies to each before *r*TMS over the left SMG with 80% and 120% of the motor threshold.

(Right) In the difference in normalized P300 latency, the positive bar indicates the reduced state and negative bar indicates the lengthened state.

3.1.4 Discussion

    Lang et al. (2006) confirmed the increase of cortical excitability by sub-threshold magnetic stimulation of the motor cortex. They also confirmed the decrease of cortical excitability by supra-threshold magnetic stimulation of the motor cortex. This study shows the same results as the study of Lang et al. The facilitation of strong cortical excitability by the extreme magnetic stimulation may lead inhibitory neurons to be activated. In contrast, the facilitation of cortical excitability by the sub-threshold magnetic stimulation may be insufficient to lead strong activation of inhibitory neurons. In the safety guideline for magnetic stimulation, a stimulation frequency of 1 Hz indicates the inhibition of cortical excitability. This guideline may not completely take the stimulation region and intensity into account. That the magnetic stimulation effect is determined only by stimulation frequency is regrettable. Therefore, the alteration of cortical excitability suggests the necessity that not only the stimulation frequency but also the stimulation intensity are considered.

3.2   *Dependence on frequency of magnetic stimulation to the supramarginal gyrus and motor cortex*

3.2.1 Introduction

The chapter 3 3.1 indicated that sub- or supra-threshold was important factor to determine the effects of 1 Hz *r*TMS to the supramarginal gyrus. However, the difference of the effect of the magnetic stimulation with sub-threshold to the supramarginal gyrus is unknown. This study observed the decrease or the increase of the cortex excitability by the low frequency *r*TMS with sub-threshold to the supramarginal gyrus. This difference of effect may be slight difference in stimulation frequency such as 1.0 and 0.5 Hz. And the effects of magnetic stimulation to the left supramarginal gyrus were different from a safe guideline of the magnetic stimulation. This difference may be lead to by magnetic stimulation intensity such as the sub- and supra-threshold. Therefore, in this chapter, the experiment by the low frequency *r*TMS with sub-threshold to the motor cortex was tried. The effects of *r*TMS with the 1.0 or 0.5 Hz were evaluated by MEP amplitude.

3.2.2 Experiment condition

Healthy right-handed subjects (1.0 Hz: six subjects, 0.5 Hz: six subjects) were enrolled in this study, ranging in age from 22 to 40 years, and, it instructed subjects to maintain muscle relaxation through the trials. The magnetic stimulation was provided to

the primary motor cortex of the left hemisphere. The MEPs induced by magnetic stimulation were measured at the right abductor pollicis brevis muscle (APB) using *Neuropack X1* (Nihonkohden, Tokyo, Japan). The sampling rate was 10 kHz, and MEP responses were band-pass filtered between 5 Hz and 3 kHz. The *Super Rapid Stimulator* (Magstim Co. Ltd.) was used as the magnetic stimulator device, with a flat figure-eight coil (70 mm diameter). rTMS was conducted using magnetic pulses with a width of 200 μs. The participant's individual motor threshold was the point at which MEPs of more than 50 μV peak-to-peak amplitude were produced in at least five of 10 successive trials (Rossini et al., 1994). rTMS was conducted with low frequency magnetic stimulation such as the 1.0 and 0.5 Hz. The experimental paradigm was divided into three phases. In this paradigm, at first, the measurement of MEP was conducted prior to intervention magnetic stimulation as a control condition. In first phase, the left motor cortex was stimulated by the total 10 pulses (0.1 Hz rTMS with 105% motor threshold). Then, 1 Hz rTMS with 80% motor threshold was applied over the left motor cortex. This second phase was stimulated by the total 100 pulses (1.0 or 0.5 Hz rTMS with 80% motor threshold). Finally, the measurement of MEP was then conducted again immediately following rTMS to evaluate the effects of magnetic stimulation. In finally phase, the left motor cortex was stimulated by the total 10 pulses (0.1 Hz rTMS with 105% motor threshold).

3.2.3 *Results*

Figure IV-3 shows MEPs before and after the intervention magnetic stimulation of 1.0 or 0.5 Hz rTMS of the motor threshold to the left motor cortex. MEP amplitude increased immediately after intervention magnetic stimulation of the 1.0 Hz compared with the control condition.

In contrast, MEP amplitude decreased immediately after intervention magnetic stimulation of the 0.5 Hz compared with the control condition (*Figure IV-4*).

Figure IV-5 shows normalized MEP amplitude by control condition. The MEP amplitude was increased by 184% at 1.0 Hz *r*TMS, and decreased by 33% at 0.5 Hz *r*TMS. With 1.0 Hz *r*TMS, MEP amplitude was significantly increased by magnetic stimulation ($p < 0.05$). With 0.5 Hz *r*TMS, MEP amplitude was significantly decreased by the magnetic stimulation ($p < 0.01$).
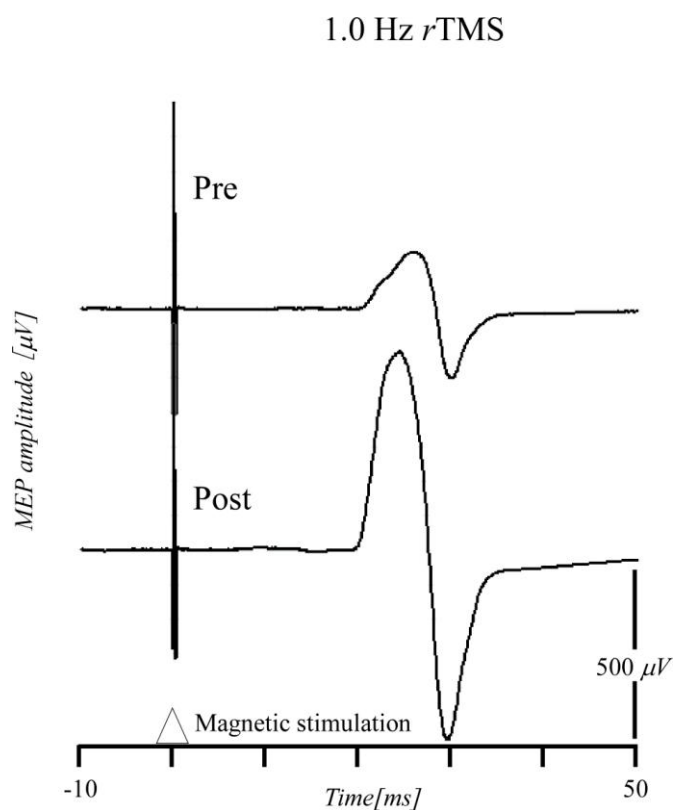
1.0 Hz *r*TMS

Figure Ⅳ-3 MEPs before and after intervention of 1.0 Hz *r*TMS with 80%

of the motor threshold over the left motor cortex.

0.5 Hz *r*TMS

Pre

Post

500 *μV*

Magnetic stimulation

-10   *Time[ms]*   50
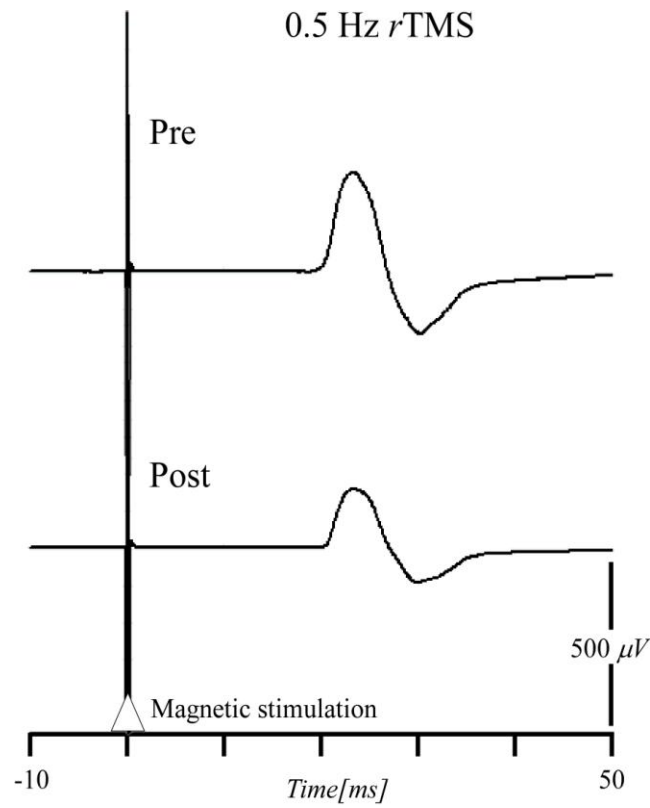
Figure Ⅳ-4 MEPs before and after intervention of 0.5 Hz *r*TMS with 80% of the motor threshold over the left motor cortex.

Significant Difference   * *p<0.05*
** *p<0.01*
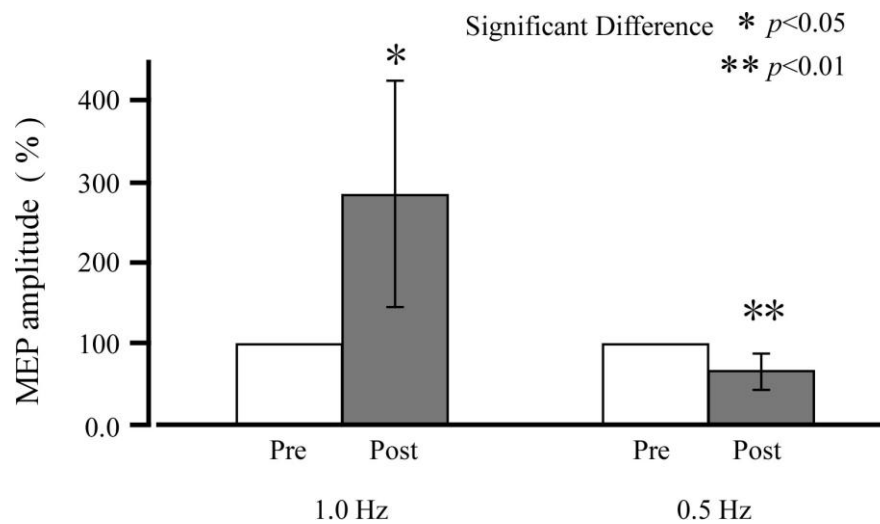
Figure Ⅳ-5 Comparison of MEP amplitude on the abductor pollicis brevis muscle (APB) by stimulating the left motor cortex with stimulation frequency at 1.0 and 0.5 Hz.

3.2.4 Discussion

Previous studies were reporting the reduction of motor cortex excitability by low frequency *r*TMS supra-threshold. Concretely, the modulation of cortex excitability was inhibited by frequency of less than 1 Hz magnetic stimulation, while was facilitated by frequency of over 5 Hz magnetic stimulation (Chen et al., 1997; Tergau et al., 1997; Wassermann et al., 1996, 1998; Pascual-Leone et al., 1998 Pascual-Leone et al., 1994b; Berardelli et al., 1998). Results of this study suggested that 1.0 Hz *r*TMS induced facilitation of motor cortex excitability, while 0.5 Hz *r*TMS induced inhibition of motor cortex excitability. These results differed from previous studies. However, this study was using magnetic stimulation intensity of sub-threshold. The effects of magnetic stimulation to the motor cortex with sub-threshold accorded with the effects of magnetic stimulation to the supramarginal gyrus. Consequently, the low frequency magnetic stimulation such as 1 Hz *r*TMS with sub-threshold may enable induction of the facilitation of cortex excitability.

Chapter 4

General discussion

General discussion

This study obtained results that both resembled and did not resemble previous research. For example, low-frequency magnetic stimulation at 1 Hz to the dorsolateral prefrontal cortex increased the P300 latency. Thus, cortical excitability can be reduced by magnetic stimulation. However, low-frequency magnetic stimulation at 1 Hz to the supramarginal gyrus shortened the P300 latency, which leads to the speculation that cortical excitability can also be facilitated by low-frequency magnetic stimulation. Here, the relevant previous research will be described in detail and compared with the results of this study. Particular attention is paid to the difference in the effects of the magnetic stimulation on motor and non-motor areas.

In Chapter 4.1, the effects of magnetic stimulation on the motor cortex are described in detail. In Chapter 4.2, the effects of magnetic stimulation on non-motor cortex are described in detail. In Chapters 4.3 and 4.4, the effects of magnetic stimulation in relation to the electroencephalogram and event-related potentials in non-motor cortex are described. In Chapter 4.5, the mechanisms of the effects of this magnetic stimulation are described. Finally, in Chapter 4.6, the possibilities of clinical applications of magnetic stimulation are described, and I assert the necessity of the development of new guidelines for the magnetic stimulation of non-motor cortex.

4.1   Study of magnetic stimulation of the motor cortex

The method of transcranial magnetic stimulation to the brain introduced by Barker et al. has been used for the diagnosis, treatment and investigation of neurological diseases of the central nervous system (Barker et al., 1985a, b). Repetitive transcranial magnetic stimulation (*r*TMS) delivered to the brain by a series or train of pulses can modify neuronal activity locally (Wassermann et al., 2001). Previous studies have indicated that the cause of the modulation of the motor evoked potential (MEP) size by *r*TMS might be the cortex (Berardelli et al., 1998). Many previous studies have reported the alteration of cortical excitability after *r*TMS. For example, a pulse of low-frequency *r*TMS less than 1 Hz reduced cortical excitability in the motor area (Chen et al., 1997; Tergau et al., 1997; Wassermann et al., 1996, 1998; Pascual-Leone et al., 1998). However, a pulse of high-frequency *r*TMS at more than 5 Hz increased cortical excitability in the motor area in several studies, and this has been demonstrated by an increase in MEP amplitude (Pascual-Leone et al., 1994b; Berardelli et al., 1998). Chan et al. stimulated the left motor cortex with 0.1 Hz *r*TMS at an intensity of 105% of the motor threshold (MT) for 1 hour (total 360 pulses). The average MEP amplitude induced from every 30 pulse stimuli over five minutes was normalized by the average of the MEP amplitude of the first 60 pulse stimuli over 10 minutes, which was defined as the control. As a result, Chen et al. demonstrated that the MEP amplitude of the right abductor pollicis brevis (APB) muscle was not significantly reduced or increased by *r*TMS for 1 hour. In another experiment, Chen et al. used 0.1 Hz *r*TMS for 15 minutes (90 pulses) before and after an intervention using *r*TMS. The intervention stimulus was 0.9 Hz *r*TMS for 15 minutes (810 magnetic stimulation pulses). The intensity of this magnetic stimulation was 115% of the motor threshold of each participant. The MEP amplitude of abductor pollicis brevis muscle was lower after *r*TMS compared with

before *r*TMS, and the MEP amplitude after this magnetic stimulation indicated a reduction of 19.5% ($p = 0.006$), which continued for 15 minutes (Chen et al., 1997).

Berardelli et al. reported a neurophysiological mechanism concerning the facilitation of MEPs after serial magnetic stimulation. The intensity of the magnetic stimulation was applied at 120% of the motor threshold. The magnetic stimulation was delivered to the motor cortex in a train of 20 stimuli of 5 Hz *r*TMS with a 1 min interval between trains. The results showed that 5 Hz repetitive magnetic stimulation to the motor cortex at an intensity of 120% motor threshold produced a transient increase in cortical excitability. In addition, the results indicated that the size of the MEP amplitude gradually increased during 5 HZ *r*TMS with 20 serial stimulations. This facilitation of cortical excitability may occur in the cortex, but not in the spinal cord. The facilitation of the cortical excitability may induce the activity of the stimulated cortical region by increasing the excitability of pyramidal cells and their excitatory inputs. In addition, the excitatory reduction of the cortical inhibition mechanism may be a factor in this facilitation effect by magnetic stimulation (Berardelli et al., 1998).

With the stimulus frequencies at 1, 3, 5, 10, 20 and 25 Hz, Pascual-Leone stimulated the motor cortex with *r*TMS at the intensity of the motor threshold. The magnetic stimulation intensity was increased gradually in steps of 10% of the motor threshold. With *r*TMS trains at 1 Hz, no consistent alteration of MEP amplitude was observed. With *r*TMS trains at 3 Hz and stimulation intensity at 150% of motor threshold, few participants showed an increase in MEP amplitude. With 5 Hz *r*TMS for 4 seconds (20 pulses), MEP amplitude gradually increased for all participants when stimulated at 150% of motor threshold. With *r*TMS at 10 Hz, MEP amplitude gradually increased for all participants at an intensity of 110–130% of motor threshold. Modulation of the amplitude of MEPs produced in the target muscle by magnetic stimulation showed effects that depended on *r*TMS frequency and intensity, such as inhibition or facilitation of cortical excitability (Pascual-Leone et al., 1994a).

Touge et al. reported that the modulation of MEP amplitude by magnetic stimulation was caused by the modification of the cortical neurons rather than the cortical synapse

(Touge et al., 2001). Previous studies have suggested that the modulation of cortical excitability may depend on stimulation parameters such as frequency, intensity, duration and intertrain interval of magnetic stimulation (Maeda et al., 2000; Touge et al., 2001). The pulses of rTMS to the cortex do not induce a small lasting effect either. These and many other results were found by performing TMS on the motor system. High-frequency rTMS of more than 5 Hz produces transient facilitation of cortical excitability, whereas low-frequency rTMS of less than 1 Hz produces transient inhibition of cortical excitability (Hallett et al., 2000; Cooke et al., 2006). The parameters used in safety guidelines for magnetic stimulation outlined by Wassermann were obtained using rTMS on the motor cortex.

However, these guidelines are also applied to the magnetic stimulation of the non-motor cortex for the following reasons. When the motor cortex is stimulated electrically, it is thought that its threshold is lower than that of other cortices (Rossi et al., 2009). Therefore this guideline may have been used safely for the non-motor cortex. However, the relationship between the excitability of the motor and non-motor cortex is unclear. Therefore, there is a possibility that the safety guidelines for magnetic stimulation of the non-motor cortex should be different than these current guidelines (Rossi et al., 2009). In terms of magnetic stimulation effects, it has been reported that an effect unlike those described in the guidelines has obtained by changing the magnetic stimulation intensity (Lang et al., 2006). Lang et al. applied 900 pulses of 1 Hz rTMS to the left motor cortex. The intensity of magnetic stimulation was 90 and 115% of motor threshold. The amplitude of the MEP was reduced by 1 Hz rTMS of 115% motor threshold on the motor cortex. This effect suggests inhibition of the cortical excitability and is in accord with Wassermann's guidelines. In contrast, Lang et al. showed that the MEP amplitude was increased by 1 Hz rTMS of 90% of the motor threshold to the motor cortex. This magnetic stimulation suggests the facilitation of cortical excitability, different from Wassermann's guidelines. Therefore, it is thought that not only the frequency of the magnetic stimulation but also the intensity is an important element in the modulation of cortical excitability. The inhibitory effects induced by 1 Hz rTMS of

the supra-threshold may result from feedback activation of the afferent neurons. When there is no or little feedback of the afferent neurons, it is thought that cortical excitability may be facilitated by *r*TMS.

4.2   Magnetic stimulation to the non-motor cortex

In most previous studies of TMS and *r*TMS, stimulation took place over the motor cortex. Alternative effects of magnetic stimulation over non-motor regions such as on cognitive function are scarcely known. In recent years, the studies of the effects of magnetic stimulation over the non-motor cortex such as the dorsolateral prefrontal cortex (DLPFC) have begun. The dorsolateral prefrontal cortex is the main stimulation region for the treatment of depression. The stimulation to a focal area of the cortex allows it to affect the region (e.g., dorsolateral prefrontal cortex) that is associated with depression. The initial treatment of depression using TMS applied a single pulse (under 0.3 Hz) from a circular coil over the vertex. Subsequently, Pascual-Leone et al. applied stimulation over the dorsolateral prefrontal cortex, which might be an important region for procedural learning (Pascual-Leone et al., 1996b; Wassermann et al., 2001). Klein et al. reported that *r*TMS at 1 Hz to the right dorsolateral prefrontal cortex was effective for patients with depression (Klein et al., 1999), and Pascual-Leone et al. showed that *r*TMS over the left dorsolateral prefrontal cortex was also effective (Pascual-Leone et al., 1996a). In contrast, Pascual-Leone reported that the application of magnetic stimulation over the right dorsolateral prefrontal cortex or other regions was ineffective for patients with depression (Pascual-Leone et al., 1996a). In the case of an application of *r*TMS to healthy participants, feelings of sadness were caused by magnetic stimulation to the left dorsolateral prefrontal cortex, whereas feelings of happiness was caused by magnetic stimulation to the right dorsolateral prefrontal cortex (Pascual-Leone et al., 1996b; George et al., 1996; Martin et al., 1997). These results suggest that dorsolateral prefrontal cortex has a lateralized function regarding human mood (George et al., 1997).

TMS has been applied to other areas than the dorsolateral prefrontal cortex.

Stimulating the occipital cortex produces phosphenes and transient scotomatous generation (Hallett et al., 2000). In previous studies, TMS was used to investigate visual cognition. Cognitive functioning may be improved or exacerbated by TMS (Grafman et al., 2000; Jahanshahi and Rothwell, 2000). Evers applied neurophysiological techniques to investigate the effects on cognitive processing by *r*TMS (Evers et al., 2001). The representative neurophysiological method to evaluate the effect of *r*TMS is electroencephalogram (EEG). In previous studies, the P300 component of the event related potential (ERP) was used to evaluate the effect on cognitive function by magnetic stimulation (Evers et al., 2000; Hansenne et al., 2000; Jing et al., 2001; Cooper et al., 2008; Iwahashi et al., 2008). However, there have been no guidelines supplied on the safe magnetic stimulation of non-motor cortical regions such as the dorsolateral prefrontal cortex. In the electrical stimulation of the cortex in the previous studies, the threshold to induce after-discharge of the motor cortex is low in comparison with the non-motor cortex. Therefore, the safety guidelines of magnetic stimulation by Wassermann have been applied to the non-motor regions. However, the threshold to induce after-discharge may be different in each cortical area, and thus the effects of *r*TMS may also differ. The optimal parameters to use for magnetic stimulation of the non-motor areas are still unclear (Rossi et al., 2009). Therefore, study is needed to obtain the optimal value of the stimulation parameters so that safe magnetic stimulation to the non-motor cortex can be provided effectively. The application of *r*TMS to the non-motor cortex according to safety guidelines is used for diagnosis and treatment, and symptoms may be improved by *r*TMS. Further, in an evaluation of the effect of treatment, the stimulation parameters of *r*TMS such as the frequency, intensity, pulse duration and stimulation site must be assessed very comprehensively for optimal effect (Klein et al., 1999).

4.3 Study of magnetic stimulation and EEG

Several studies have reported the influence of *r*TMS on EEG. Many papers have described studies on how to guard against epileptiform abnormality during or after magnetic stimulation (Loo et al., 2001; Boutros et al., 2000, 2001; Fregni et al., 2005, 2006; Cantello et al., 2007; Joo et al., 2007; Conte et al., 2007; Menkes and Gruenthal et al., 2000; Steinhoff et al., 1993; Hufnagel and Elger 1991; Kanno et al., 2001, Huber et al., 2007; Jahanshahi et al., 1997; Wassermann et al., 1996). Moreover, most of these studies applied the *r*TMS stimulation protocol according to Wassermann's safety guidelines. The influence of *r*TMS on EEG continues for a while after magnetic stimulation, and the period of influence accords with the continuance of the motor cortical excitability (Rossi et al., 2009). In most TMS and EEG studies, low-frequency *r*TMS leads to the inhibition of cortical excitability, whereas high-frequency *r*TMS leads to its facilitation. The effects of magnetic stimulation and their duration may be similar regardless of whether the stimulation position was on the motor cortex or the non-motor cortex. However, in cortex related to cognition, several studies have shown effects unlike those found in the motor cortex (Jing et al., 2001; Evers et al., 2001; Hansenne et al., 2004, Rossi et al., 2001, 2006, 2009). The modulation mechanism of the cognition function by the magnetic stimulation is unclear. However, it is estimated that the alteration of cortical excitability by magnetic stimulation may affect the recognition function. Therefore, slight variations in a stimulation parameter may induce an opposite effect. Furthermore, magnetic stimulation may have slightly different effects on different regions of the brain such as the motor cortex, supramarginal gyrus and dorsolateral prefrontal cortex.

4.4 Study of magnetic stimulation and event-related potentials

The effects of *r*TMS are evaluated not only by the alteration of MEP amplitude (Chen et al., 1997; Wassermann et al., 2001; Berardelli et al., 1998) but also by the improvement of visual cognition (Kammer and Nusseck, 1998), speech arrest (Pascual-Leone et al., 1991; Jennum et al., 1994; Epstein et al., 1996), the modulation of mood (Triggs et al., 1999; Pascual-Leone et al., 1996a, b; George et al., 1996; Martin et al., 1997) and so on. To explain these results, it was suggested that the modulation in the neuronal network affects physiological function (Jing et al., 2000). However, the alteration of audibility ERPs after magnetic stimulation is scarcely known. ERP components such as N100, P200, N200 and P300 are a cerebral response induced by cognitive functional activity, such as vision and audition. The oddball paradigm, a task where the participant must recognize a rarely-presented target signal, is used to elicit the P300 component. It is thought that the nervous electrical phenomenon of the cognition process causes the P300 component (Polich and Kok, 1995; Kugler et al., 1996). It is also thought that the P300 component may be caused by the process of cortical activity itself (Johnson, 1993). The P300 component is usually measured to evaluate its amplitude (size) and latency (time). It was thought that the appearance probability of the target stimulus, the importance of the stimulus, the difficulty of the task, the motivation of the participant and the attention of the participant affect the P300 amplitude, while the time needed for cognitive processing affects the P300 latency (Yasukouchi et al., 1995; Kugler et al., 1996; Geisler et al., 1999). The P300 latency is the time when the peak amplitude of the positive wave is elicited – approximately 250–400 ms after target stimulation in the oddball task, as defined by Polich and Kok. It is thought that the

appearance range of the P300 component is altered based on the target stimulation type and the age of the participants (Polich and Kok, 1995). Therefore, the P300 latency reflecting cognitive processing is the component that is important for the evaluation of cognitive functioning.

Jing et al. investigated the effects of *r*TMS on cognitive processing by measuring audibility ERPs using an oddball paradigm with healthy volunteers (Jing et al., 2001). The effect of the magnetic stimulation was evaluated by comparing ERPs, such as the latency and amplitude of the N100, P200, N200 and P300 components, before and after *r*TMS. The number of stimulation times was a total of 60 pulses with a stimulation frequency of 10 Hz and a stimulation intensity of 100% of the motor threshold. They found that a significant delay was induced in P300 latency after the magnetic stimulation compared with before the magnetic stimulation. The delay in the P300 latency may have resulted from the influence (inhibition) on the cortical network by the magnetic stimulation. Jing et al. put forward the possibility that the effects of *r*TMS on cognitive functioning (Jahanshahi et al., 1997; Triggs et al., 1999; Pascual-Leone et al., 1994a) were inconsistent with the effects that the safety guidelines for magnetic stimulation were based on. This contradiction was suggested when Jing et al. found that *r*TMS on the left dorsolateral prefrontal cortex showed contrasting results to those that yielded from the stimulation of other cortices, such as the motor cortex. In their results, Jing et al. demonstrated that the region stimulated by *r*TMS induced a P300 latency delay by altering information connections. Therefore, these results suggested that magnetic stimulation might affect neuronal activity related to cognitive processing. In addition, Jing et al. suggested that a stimulation parameter was paradoxical (Jing et al., 2001).

Evers et al. investigated the possibility that neurophysiological measurements could be used to investigate the influence of *r*TMS on cognitive processing. This study applied 1 Hz *r*TMS over the dorsolateral prefrontal cortex for two minutes (120 total pulses). They applied *r*TMS (95% motor threshold) at 20 Hz over the dorsolateral prefrontal cortex. The stimulation was three series of a period of 5 s, which totaled 300

pulses with a 1-min break between two trains. The visual oddball paradigm was used to measure the P300 component of the ERPs. The effects of the magnetic stimulation were evaluated by measuring the difference in the P300 latency between sham and post-stimulation. They demonstrated that a reduction in P300 latency was caused after 20 Hz *r*TMS to the left dorsolateral prefrontal cortex. In contrast, the P300 latency after 1 Hz *r*TMS over the dorsolateral prefrontal cortex was unchanged. These results contradicted the report by Jing. The magnetic stimulation by Jing et al. showed an inhibitory effect on cognitive processing. The effect of the magnetic stimulation on cognitive processing by Evers et al. elicited facilitation rather than the inhibition. Evers et al. suggested that the effect of low-frequency *r*TMS at 1 Hz to the dorsolateral prefrontal cortex was different from the effect predicted by the safety guidelines for magnetic stimulation. In addition, they suggested that the dorsolateral prefrontal cortex might contribute to the generation of the P300 component (Halgren et al., 1998; Linden et al., 1999). Several reports have shown that a role of left hemisphere areas such as the left prefrontal region is to produce a P300 component (Halgren et al., 1998; Linden et al., 1999). The modulation of the P300 latency by the magnetic stimulation to the left prefrontal region may clarify these claims (Evers et al., 2001).

Hansenne et al. measured ERPs before and after 1 Hz *r*TMS to the prefrontal area to evaluate the effects of magnetic stimulation, with a stimulation intensity of 100% motor threshold and either 600 or 900 stimulus pulses (Hansenne et al., 2004). In this study, the P300 latency was delayed after the magnetic stimulation for 15 minutes (900 magnetic pulses). When magnetic stimulation was only used for 10 minutes (600 magnetic pulses), neither an increase nor a decrease in P300 latency was obtained. However, no effects of *r*TMS were discovered on early components of ERP such as the amplitude and latency of N100, P200 and N200. These results accord with Jing and Evers (Jing et al., 2001; Evers et al., 2001). The increases in P300 latency suggest the inhibition of cortical excitability by 1 Hz *r*TMS over 15 minutes (900 magnetic pulses). Hansenne et al. suggest that *r*TMS alters the speed of cognitive processing rather than the aggressiveness of information processing. Therefore, it is thought that the inhibition

of cortical excitability induced by magnetic stimulation is affected by a controlled cognition process and is not automatic (Hansenne et al., 2004).

Cooper et al. also applied 1 Hz *r*TMS for 15 minutes (900 magnetic pulses) over the right dorsolateral prefrontal cortex. In the same way as in the previous study, the P300 component was measured to evaluate the effect of *r*TMS on cognitive processing (Cooper et al., 2008). 1 Hz *r*TMS over the right dorsolateral prefrontal cortex did not produce significant modulation of the P300 latency, which agrees with the results of Evers (Evers et al., 2001).

Therefore, these results demonstrate the possibility that the results obtained when delivering *r*TMS to the motor cortex cannot apply to the non-motor cortex. In addition, these results suggest that slight differences in stimulation parameters may induce an opposite effect (Rossi et al., 2009).

The magnetic stimulation protocols in this study were 1.00, 0.75, 0.50 or 0.25 Hz of stimulus frequency, and the magnetic stimulation sites were the supramarginal gyrus (SMG) or dorsolateral prefrontal cortex. With 1 Hz low-frequency magnetic stimulation to the dorsolateral prefrontal cortex, these were the same as in the paper by Hansenne (Hansenne et al., 2004). However, the modulation of stimulus frequency and site were different from the previous study. In particular, the effect of *r*TMS to the left supramarginal gyrus was different compared with the motor cortex. Previous studies suggested that slightly different conditions might induce different effects. In 1 Hz *r*TMS at 90% of motor threshold, few studies reported an increase (the facilitation of the cortical excitability) of the amplitude of MEPs in the motor cortex. Lang et al. suggested that the inhibitory effect induced by 1 Hz *r*TMS of the supra-threshold might result from feedback activation of the afferent neurons (Lang et al., 2006). The facilitation effect induced by 1 Hz *r*TMS of the sub-threshold may not be affected by the feedback of the afferent neurons. The magnetic stimulation may induce the opposite effect depending on the stimulation intensity. Therefore, in the chapter 3 3.1, magnetic stimulation at 120% of the motor threshold was applied to the supramarginal gyrus to examine the relationship between magnetic stimulation effects and intensity. The P300

latency was measured before and after magnetic stimulation intervention to evaluate the magnetic stimulation effect at 120% of the motor threshold. The result of this experiment was accorded with safety guideline of magnetic stimulation. In addition, the left motor cortex was stimulated by 1.0 or 0.5 Hz *r*TMS with sub-threshold. And, the modulation of MEP amplitude was observed to evaluate the cortex excitability. The results of this experiment were compared with the results of the magnetic stimulation to the left supramarginal gyrus. Effects of the magnetic stimulation to motor cortex with sub-threshold accorded with effects of magnetic stimulation to the left supramarginal gyrus (see the chapter 2), while the result was not accorded with safety guideline of magnetic stimulation.

Furthermore, in this study, it is thought that the left dorsolateral prefrontal cortex is associated with the generation of the P300 component, and it is speculated that the left supramarginal gyrus strongly participates in the generation of the P300 component compared with the other regions. When magnetic stimulation is applied in a clinical setting, it is thought that an optimal protocol of magnetic stimulation for the required stimulation site is necessary.

4.5   Mechanism of the magnetic stimulation

The activation of neuronal axons by magnetic stimulation may modulate cortical excitability (Rothwell, 1997). The alteration of the MEP amplitude may be induced by the excitatory alteration of cortical neurons, but not by the effect of the cortical synapses (Touge et al., 2001). The magnetic fields induced by TMS or *r*TMS generate eddy currents in the brain and can modulate cortical excitability, such as the facilitation or inhibition, of localized regions. It is thought that magnetic stimulation of the motor cortex is effective in inhibiting muscle contraction and movement. Moreover, TMS over the visual area of the occipital cortex can induce phosphenes or transient scotoma (Amassian et al., 1989). *r*TMS can cause modulation of cerebral function that is longer than the magnetic stimulation period (Hallett et al., 2000; Cooke et al., 2006). A mechanism similar to long-term depression (LTD) or long-term potentiation (LTP) may contribute to this long-term effect (Wang et al., 1996; Chen et al., 1997; Wassermann 1998; Hallett 2007; Hallett 2000; Maeda et al., 2000; Touge et al., 2001; Wassermann and Lisanby 2001; Ziemann et al., 2001; Lee et al., 2003; Thickbroom et al., 2006; Cooke et al., 2006; Hamada et al., 2007; Ridding and Rothwell, 2007). If the effect is not related to magnetic stimulation, the modulation of cortical excitability should disappear just after the magnetic stimulation stops (Ridding and Rothwell, 2007).

However, the precise mechanism responsible for the long-term modulation of cortical excitability such as facilitation or inhibition is unclear. Long-term potentiation strengthens the connection with the presynaptic membrane while long-term depression weakens the connection with the presynaptic membrane. Therefore the effects of magnetic stimulation suggest possibilities for the rehabilitation and treatment of psychiatric disorders and so on (Ziemann et al., 1998). In this study, the effect of *r*TMS was in fact longer than the stimulation period. Therefore, magnetic stimulation affects

the cortex directly, and the LTP/LTD-like effect suggests the possibility of indirect action.

In a previous study, the continuance of the effect by the low-frequency magnetic stimulation for the motor cortex was around 15 minutes (Chen et al., 1997; Touge et al., 2001). In these reports, the effects of magnetic stimulation were obtained after around 1000 pulses. For high-frequency magnetic stimulation at 5 Hz after 1800 pulses, the effect continued for around 30 minutes (Peinemann et al., 2004). It is thought that the effects of magnetic stimulation and their duration may be similar regardless of whether the stimulation position was on the motor cortex or the non-motor cortex (Rossi et al., 2001, 2006, 2009).

4.6   Clinical application of magnetic stimulation

The modulation of cortical excitability via *r*TMS continues for a while after the magnetic stimulation has stopped (Hallett et al., 2000; Cooke et al., 2006). Pascual-Leone et al. suggested that high-frequency and high-intensity *r*TMS can induce an epileptic seizure (Pascual-Leone et al., 1991; Dhuna et al., 1991; Hufnagel and Elger, 1991; Tergau et al., 1999; Wassermann et al., 1996, 1998). In contrast, low-frequency *r*TMS shows an inhibitory effect of epileptic activity. Therefore, the epileptic elicitation risk is low for low-frequency *r*TMS, and this may be helpful for clinical application (Klein et al., 1999; Kinoshita et al., 2005; Misawa et al., 2005).

*r*TMS has been used in the treatment of depression and has shown an antidepressant effect. Therefore, *r*TMS may be helpful for the treatment or the reduction of symptoms of depression (George et al., 1997). George et al. demonstrated that an application of 20 Hz *r*TMS (80% of the motor threshold) every day for 10 days to the left prefrontal region was helpful for patients with depression.

However, Pascal-Leone et al. found that 10 Hz *r*TMS (90% of the motor threshold) over the right prefrontal cortex did not show an antidepressant effect (Pascual-Leone et al., 1996a). The difference in these effects may be attributed to a stimulation parameter. It is thought that the differences in these effects were caused by the different stimulation region. In healthy participants, *r*TMS to the prefrontal cortex induces modulation of the lateralized mood. In particular, an increase in happiness is induced by stimulation of the right prefrontal area, while sadness is increased by stimulating the left prefrontal area (Pascual-Leone et al., 1996; George et al., 1996; Martion et al., 1997). *r*TMS enables focal stimulation less than 5 mm (Ueno et al., 1990). Therefore, it is thought that stimulation to the specific brain region is needed to obtain the required effects.

*r*TMS has improved the symptoms of Parkinson's disease such as bradykinesia, and

the therapeutic effects of *r*TMS lasted for a long time after treatment ended (Pascual-Leone et al., 1994a, Siebner et al., 1999, 2000; Lefaucheur et al., 2004; Khedr et al., 2003; Lomarev et al., 2006; Fregni et al., 2005). *r*TMS is also known to be efficacious in the treatment of stroke (Khedr et al., 2005; Murase et al., 2004; Talelli et al., 2007; Takeuchi et al., 2005; Kim et al., 2006), dystonia (Siebner et al., 1999; Murase et al., 2005; Huang et al., 2004), tinnitus (Kleinjung et al., 2005; Langguth et al., 2003), neurogenic pain (Khedr et al., 2005; Lefaucheur et al., 2001), amyotrophic lateral sclerosis (Di, Lazzaro et al., 2006), schizophrenia (Lee et al., 2005; Chibbaro et al., 2005), addiction (Camprodon et al., 2007; Eichhammer et al., 2003), obsessive-compulsive disorder (Greenberg et al., 1997; Sachdev et al., 2001) and memory dysfunction (Sole-Padulles et al., 2006).

In addition, the P300 component of the ERP is used for the study of cognition processing for healthy participants and in psychopathology (Bruder et al., 1991; Diner et al., 1985; Gangadhar et al., 1993; Gordon et al., 1986; Have et al., 1991; Picton, 1992). It is thought that the P300 latency reflects the time for stimulation evaluations such as in audition and vision and so on (Kutas et al., 1977), and may be useful in the study of depression (Hansenne et al., 2000).

For example, TMS is applied to the treatment of depression, and P300 latency may be useful for the evaluation of the effect of treatment. However, even for a healthy participant, an epileptic seizure may be induced by an increase of cortical excitability by high-frequency or high-intensity *r*TMS (Wassermann 1998). Therefore, low-frequency and low-intensity magnetic stimulation is important to reduce the risk of epileptic seizures during treatment using *r*TMS. This study measured P300 latency to evaluate the effects of low-frequency or low-intensity *r*TMS on cognitive function. It is speculated that the data of this study have value in the future safety clinical application of *r*TMS. In addition, this study can contribute to the production of safety guidelines for the magnetic stimulation of non-motor cortical areas, such as those involved in cognitive function.

Conclusion

The present study clarified the effects of repetitive transcranial magnetic stimulation (rTMS) on regional brain activity. The latency of the P300 component of induced event-related potentials (ERPs) was used to evaluate the effects of low-frequency and short-term rTMS by stimulating the bilateral supramarginal gyrus (SMG) and dorsolateral prefrontal cortex (DLPFC).

rTMS was conducted with 1.00, 0.75, 0.50, and 0.25 Hz stimulation, and 1.00 and 0.50 Hz sham stimulation, and was performed using 100 magnetic pulses. The width of each pulse was 200 μs and the strength of the magnetic stimulation was set to 80% of the participant's motor threshold (MT). The latency of the P300 component of the ERPs was elicited by an auditory oddball task. ERP data were measured at the Fz, Cz and Pz electrodes according to the international 10–20 electrode system by an Ag/Ag-Cl electrode.

Jing et al. demonstrated that magnetic stimulation might affect neuronal activity related to cognitive processing. Hansenne et al. demonstrated that the inhibition of cortical excitability by 1 Hz rTMS over 15 minutes induced the increases in P300 latency. In contrast, it is thought that the facilitation of cortical excitability by rTMS decreased P300 latency. In the previous studies, the alteration of the P300 latency by magnetic stimulation was linked to alteration of the cortex excitability. Therefore, in this study, it was thought that the effect by the magnetic stimulation to the P300 latency was changed by cortex excitability. Moreover, in the case of magnetic stimulation for the non-motor cortex in the previous studies, the motor threshold was applied to the magnetic stimulation intensity. As for the previous studies, movement threshold is considered with criteria. In this study, the motor threshold was applied to the magnetic stimulation intensity according to previous studies.

The results revealed differing effects on P300 latencies following 1.00, 0.75, 0.50 and 0.25 Hz rTMS over the left supramarginal gyrus, and differing effects on P300 latencies

following 1.00, 0.75 and 0.50 Hz *r*TMS over the left dorsolateral prefrontal cortex. These findings indicate that the effects of *r*TMS over the left supramarginal gyrus and dorsolateral prefrontal cortex were frequency-dependent. The results also demonstrated that *r*TMS over the right supramarginal gyrus and dorsolateral prefrontal cortex had no significant effects on P300 latencies and were therefore not frequency-dependent.

Based on the results of this study, I propose the following process of neuronal excitement after the magnetic stimulation. A neuron is initially excited by *r*TMS, which results in the excitation of inhibitory neurons, and the excited neurons then return to a resting state or are inhibited. It is thought that this inhibited state gradually returns to the resting state. In this study, the neurons were exposed to 1 Hz magnetic stimulation, the transition from a strong excited condition to the resting state or inhibitory state may be difficult. However, if very strong neuronal excitability is obtained by magnetic stimulation of the supra-threshold, the cortical excitability may show an inhibitory effect based on forced activity of the inhibitory neurons.

Magnetic stimulation at 1 Hz is known to modulate the excitability of the motor cortex to inhibition, while magnetic stimulation at 5 Hz modulates the excitability of the motor cortex to facilitation. However, in this study, low-frequency magnetic stimulation at 1 Hz for the supramarginal gyrus produced a facilitation effect on the cortical excitability. Therefore, this study suggests that magnetic stimulation might have slightly different effects on different regions of the brain such as the motor cortex, supramarginal gyrus and dorsolateral prefrontal cortex.

Normally, it is thought that magnetic stimulation at low frequency such as a stimulation frequency of 1 Hz induces inhibitory effects on cortical excitability. The results of this study differed from the safety guidelines generally used for magnetic stimulation. The facilitation effect on cortical excitability at low-frequency magnetic stimulation was confirmed in the motor cortex (Lang et al., 2006). The supra-threshold low-frequency *r*TMS of 1 Hz activates afferent neurons, and the feedback by these afferent neurons induces inhibition of cortical excitability. In contrast, for the sub-threshold low-frequency *r*TMS of 1 Hz, the afferent neurons may not be as strongly

activated. Therefore, it is thought that the depression of cortical excitability may not be induced by low-frequency sub-threshold magnetic stimulation. For low-frequency *r*TMS at 80% of the motor threshold over the left supramarginal gyrus, strong inhibition may not be induced by cortical excitability. In fact, low-frequency *r*TMS to the left supramarginal gyrus with the 120% motor threshold induced a delay in the P300 latency. Thus, the effect of cortical excitability may depend on stimulation site, frequency and intensity. Previous studies were reporting the reduction of motor cortex excitability by low frequency *r*TMS supra-threshold. However, the results of this study differed from previous studies. Concretely, the results of this study suggested that 1.0 Hz *r*TMS induced facilitation of motor cortex excitability, while 0.5 Hz *r*TMS induced inhibition of motor cortex excitability. The effects of magnetic stimulation to the motor cortex with sub-threshold accorded with the effects of magnetic stimulation to the supramarginal gyrus. As a result of this study, the low frequency magnetic stimulation such as 1.0 Hz *r*TMS with sub-threshold may enable induction of the facilitation of cortex excitability. Consequently, the cortical excitatory facilitation by low-frequency magnetic stimulation can provide safer than high-frequency magnetic stimulation.

Acknowledgements

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