34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Time-Dependent Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Supramarginal Gyrus

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Abstract— **In this paper, we report our studies of the effects of stimulating the bilateral supramarginal gyrus (SMG) with low-frequency transcranial magnetic stimulation (rTMS) or short-term rTMS on brain excitability in humans. We analyzed the effects of various durations of stimulation on P300 latencies of the event-related potential (ERP). Magnetic pulses were delivered using a figure-eight flat coil. The intensity of rTMS was set to 80 % of the subject's motor threshold. In each round of rTMS, 100 magnetic pulses were applied over the scalp at frequencies of 1.00, 0.75, and 0.50 Hz. ERPs were measured prior to magnetic stimulation as a control. The effects of magnetic stimulation were then determined by measuring its effects on P300 latencies elicited by an odd-ball task. These latencies were measured before and 0, 5, 10, and 15 min after the magnetic stimulation. 1.00 Hz low-frequency rTMS of the left SMG decreased P300 latencies for approximately 10 min. In contrast, 0.50 Hz rTMS of the left SMG resulted in delayed P300 latencies for approximately 15 min. We furthermore found that 0.75 Hz rTMS of the left SMG and 1.00, 0.75 and 0.5 Hz rTMS of the right SMG did not affect P300 latencies. These results suggest that the duration of the effects of rTMS depend on the frequency of stimulation.**

I. Introduction

Transcranial magnetic stimulation (TMS) is a neurodiagnostic tool that was developed in 1985 [1], [2]. TMS has been used to map regional functions of the cortex [3], [4]. In recent years, TMS and repetitive transcranial magnetic stimulation (rTMS) have attracted attention for the treatment and study of cerebral function. rTMS has been applied to the human brain [5]. TMS and rTMS are very important devices [6]. TMS, rTMS and electroconvulsive therapy (ECT) can stimulate the brain. ECT is affected by the high-impedance of the skull, skin and hair. However, TMS and rTMS are not affected by these. The magnetic fields can induce an electric current in the cortex of the brain by non-infestation. This induced electric current is required to alter neuronal activity [7]. Most studies of the effects of TMS and rTMS have focused on the motor evoked potential (MEP) or event-related potential (ERP) [8]-[15]. MEPs can be used to assess the effects of magnetic stimulation in motor areas, but only in motor areas. Fortunately, the ERP can be used to assess the effects of rTMS in sensory areas. For instance, previous studies have reported a delay in P300 latencies when TMS was applied 200 or 250 ms after odd-ball sound stimulation. These results suggest that the left supramarginal gyrus (SMG) contributes to the generation of the P300 component at around 200 ms after odd-ball stimulation [16]. In contrast, low-frequency rTMS of the right dorsolateral prefrontal cortex (DLPFC) produced no significant alteration in P300 ERP components before and after magnetic stimulation [17]. However, no effect of low-frequency rTMS has been investigated in detail. Therefore, in this study, we sought to determine the effects of low-frequency rTMS on P300 latencies in detail, and to clarify the duration of these effects.

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II. Methods

The measurement system was a STIM2 from NeuroScan Co. Ltd, which produced the trigger signals and stimulation sounds. The trigger signal was used to start the electroencephalography (EEG) measurements, and the stimulation sounds were used for the odd-ball task. The task in this study was composed from 3 processes. In this task, an odd-ball presentation was given prior to magnetic stimulation as a control, rTMS was then applied to the left or right SMG, and the odd-ball task was then executed again at 0, 5, 10 and 15 min after rTMS to evaluate the effects of the magnetic stimulation.

Two different pure tones were used in the odd-ball task. A pure tone of 1 kHz was the non-target stimulation sound, which was presented in 80% of the trials. A pure tone of 2 kHz was the target stimulation sound, which was presented in 20% of the trials. The sounds were presented randomly. The stimulation sounds lasted 50 ms, were burst waves, and had an intensity of 60 dB. The interval between stimulation sounds was 2,500 ms.

EEG measurements were conducted at the Fz, Cz, and Pz electrodes, based on the international 10-20 electrode system. The polar contact impedance was set to less than five kilo ohms. EEG measurements were started by a trigger signal, and were recorded for 1 second. The sampling frequency was 1,000 Hz and the synchronized sum was 20 times. A digital band pass filter of 0.5–50 Hz was applied to the data.

A figure-eight shaped flat coil (70 mm diameter) served as the stimulation device (MAGSTIM). The stimulation was performed over 100 pulses of a 2 ms duration each, and at a frequency of 1.00, 0.75 or 0.50 Hz. The stimulus intensity was 80% of subject's motor threshold. A total of 10 healthy, right-handed volunteers were enrolled in the study, and their

ages ranged from 23 to 38 years of age. For testing, the subjects were asked to relax and sit in a chair.

III. Results

Fig.1 to 3 illustrate the ERPs of one subject. Fig.1 shows ERPs at the Cz electrode before and after 1.00 Hz stimulation of the left SMG, which shortened P300 latencies. Compared with the control condition, immediately after magnetic stimulation, P300 latencies were shorter by 10.9 ms at the Fz electrode, 8.7 ms at the Cz electrode, and 15.4 ms at the Pz electrode. 5 min after the magnetic stimulation, P300 latencies were shorter by 8.4 ms at the Fz electrode, 15.2 ms at the Cz electrode, and 18.4 ms at the Pz electrode. However, at 10 and 15 min after magnetic stimulation, there was no difference in P300 latencies compared with the control conditions (10 min: 2.0 ms at the Fz electrode, 3.0 ms at the Cz electrode, 2.8 ms at the Pz electrode; 15 min: 1.5 ms at the Fz electrode, 4.0 ms at the Cz electrode, 1.2 ms at the Pz electrode). This decrease in P300 latencies continued for 10 min after the rTMS. Fig. 2 shows ERPs at the Cz electrode before and after 0.75 Hz stimulation of the left SMG, which did not alter P300 latencies. Fig. 3 shows ERPs at the Cz electrode before and after 0.50 Hz stimulation of the left SMG, which resulted in delayed P300 latencies. Compared with the control condition, rTMS delayed P300 latencies by 13.3 ms at the Fz electrode, 8.2 ms at the Cz electrode, and 8.8 ms at the Pz electrode. 5 min after the odd-ball task, rTMS delayed P300 latencies by 22.8 ms at the Fz electrode, 21.5 ms at the Cz electrode, and 22.3 ms at the Pz electrode. 10 min after the odd-ball task, rTMS delayed P300 latencies by 22.3 ms at the Fz electrode, 16.2 ms at the Cz electrode, and 8.6 ms at the Pz electrode. In contrast, 15 min after rTMS there was no difference in P300 latencies compared with the control conditions (Fz: 6.5 ms, Cz: 0.5 ms, Pz: 3.3 ms). This increase in P300 latencies

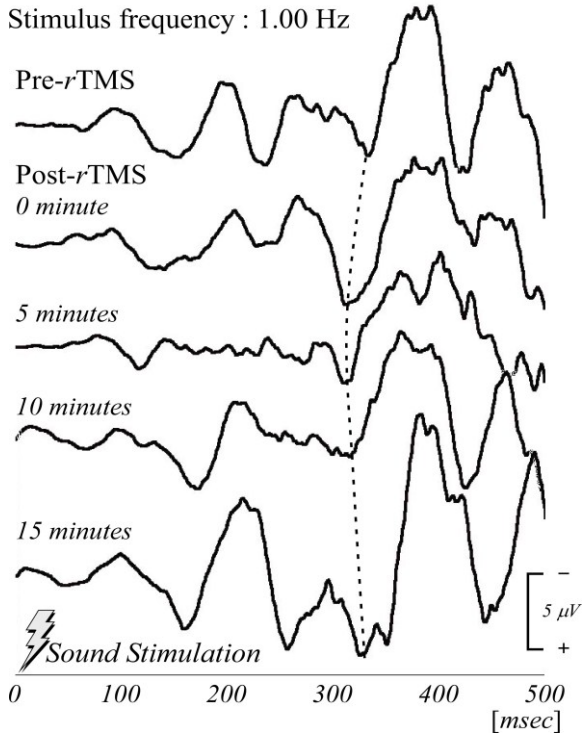

Figure 1. ERPs at the Cz electrode before and after rTMS of the left SMG at 1.00 Hz.

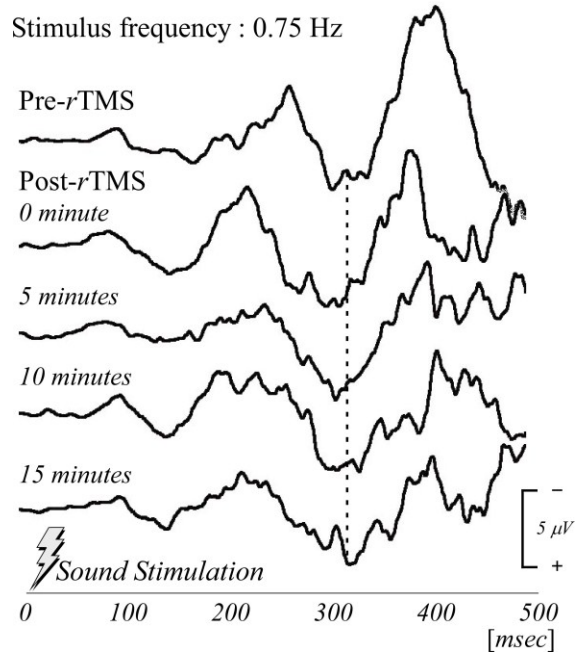

Figure 2. ERPs at the Cz electrode before and after rTMS of the left SMG at 0.75 Hz.

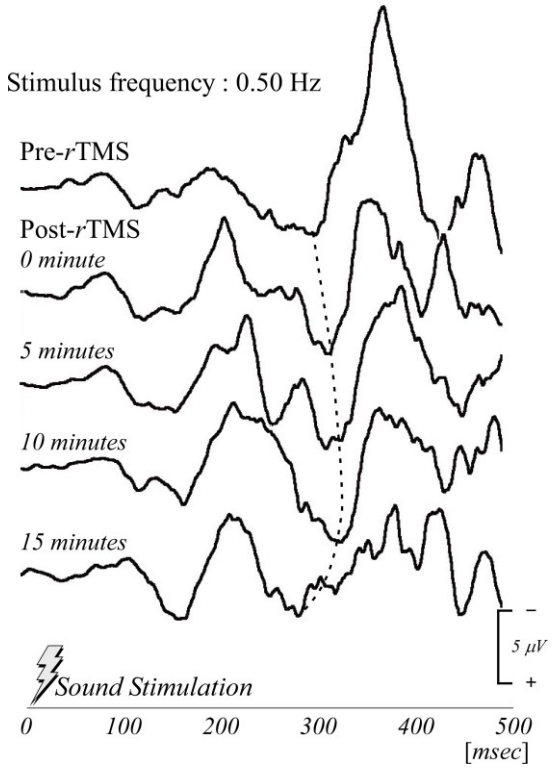

Figure 3. ERPs at the Cz electrode before and after rTMS of the left SMG at 0.50 Hz.

continued for 15 min after the rTMS. Fig.4 and Fig.5 show P300 latencies normalized to the control condition for the left and right SMG. These figures are representing the average of P300 latencies for all the subjects. In contrast to these effects in the left SMG, rTMS of the right SMG had no significant effect on P300 latencies regardless of the stimulation frequency.

IV. Discussion

Previous studies have confirmed that slow or low frequency magnetic stimulation decreases cortical excitability and fast or high frequency magnetic stimulation increases cortical excitability [18]-[20]. Therefore, we hypothesized that low-frequency magnetic stimulation would delay P300 latencies. Consistent with this hypothesis, P300 latencies were delayed after 0.50 Hz stimulation of the left SMG. However, shortening of P300 latencies was observed following 1.00 Hz magnetic stimulation of the left SMG. These results suggested that 1.00 Hz rTMS magnetic stimulation excited the cerebral cortex. In contrast, stimulation of the left SMG at 0.75 Hz did not change P300 latencies. These results suggest that the effects of rTMS on P300 latencies depend on the frequency of stimulation.

In contrast to the left SMG, rTMS of the right SMG had no significant effects on P300 latencies. The left SMG has been shown to be involved in P300 generation [21]. These results suggest that the left SMG is more susceptible to magnetic stimulation than the right SMG. Similarly,

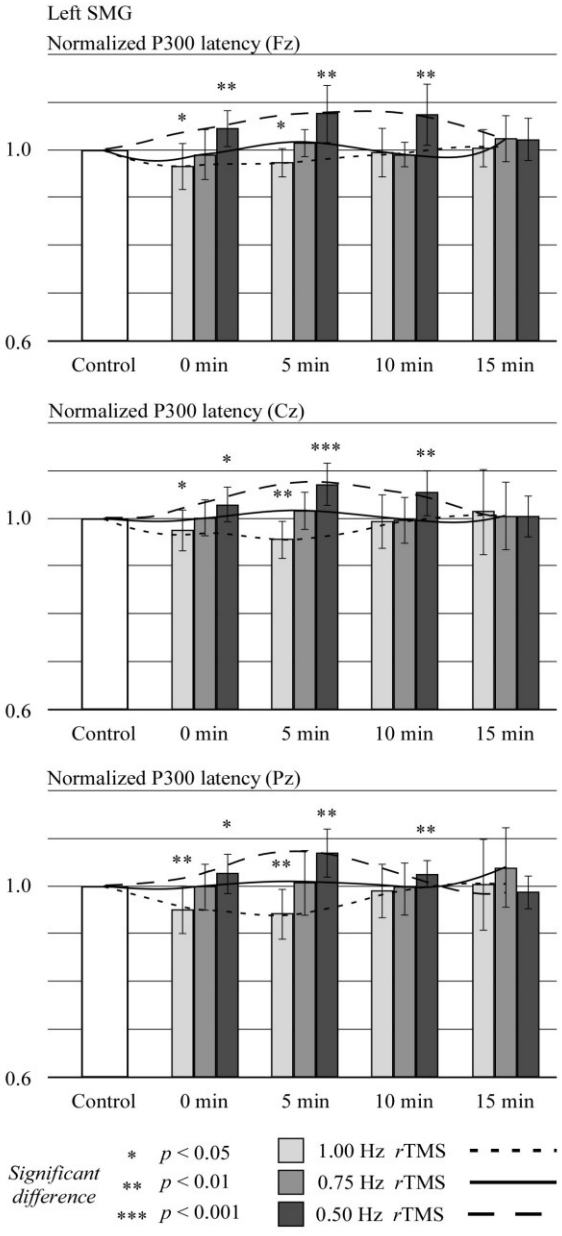

Figure 4. Normalized P300 latencies at the Fz (top), Cz (middle), and Pz (bottom) electrodes before and after stimulation of the left SMG.

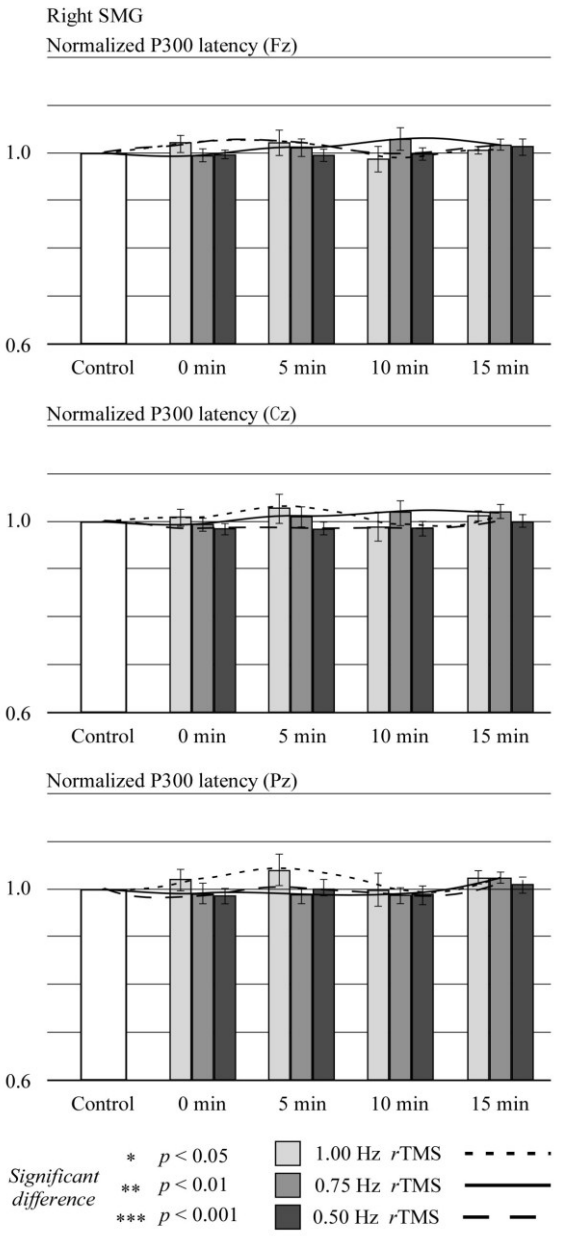

Figure 5. Normalized P300 latencies at the Fz (top), Cz (middle), and Pz (bottom) electrodes before and after stimulation of the right SMG.

frequency-dependent effects of rTMS of the left DLPFC have been reported [22].

A recent study showed that neuronal excitement was induced by effects of rTMS on excitatory synapses [23], [24]. Accordingly, we propose the following process of neuronal excitement after magnetic stimulation. A neuron is initially excited by rTMS, this results in excitation of inhibitory synapses, and the excited neurons then return to a resting stage or are inhibited. In this study, an inhibited state was induced by 0.50 Hz rTMS of the left SMG. In contrast, a return to the resting stage was induced by 0.75 Hz rTMS of the left SMG or 0.50, 0.75 and 1.00 Hz rTMS of the right SMG. This inhibited state gradually returns to the resting stage. If neurons are exposed to high-frequency magnetic stimulation, even at inhibitory synapses, the transition from a strong excited condition to the resting state or inhibitory state may be difficult. In this study, 1.00 Hz rTMS of the left SMG induced a sustained excited condition. This excited state can be returned to the resting stage by inhibitory synapses. Therefore, the present results demonstrate that although P300 latencies following magnetic stimulation have a shorter return time to the resting state, there was a delay in the recovery of the resting state when P300 latencies were extended by magnetic stimulation.

V. Conclusion

In this study, we sought to determine the effects of rTMS on brain activity. The P300 latency of the ERP was used to evaluate the effects of stimulating the left or right SMG. We found different effects on P300 latencies by 1.00, 0.75, and 0.50Hz rTMS of the left SMG. Therefore, the results obtained in this paper suggest that the effects of rTMS on the left SMG are frequency dependent. In contrast, rTMS of the right SMG was not frequency dependent. Moreover, the results demonstrate the rTMS-induced shortening of P300 latencies lasts for 10 min, whereas rTMS-induced increases in P300 latencies last for 15 min. Therefore, these results suggest that the effects of rTMS are also time dependent.

References

[1] A. T. Barker, I. L. Freeston, R. Jalinous, P. A. Merton, and H. B. Morton, "Megnetic stimulation of the human brain," *J. Physiol*, vol. 369, p. 3, July, 1985.

[2] A. T. Barker, R. Jalinous and I. L. Freeston, "Non-invasive magnetic stimulation of human motor cortex," *Lancet*, vol. 1, pp.1106-1107, May 1985.

[3] T. Paus, R. Jech, C. J. Thompson, R. Comeau, T. Peters and A. C. Evans, "Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex," *J Neuroscience*, vol. 17(9), pp. 3178-3184, May, 1997.

[4] A. Pascual-Leone, E. M. Wassermann, J. Grafman and M. Hallett, "The role of the dorsolateral prefrontal cortex in implicit procedural learning," *Exp Brain Res*, vol. 107, pp. 479-485, 1996.

[5] A. Pascual-Leone, J. R. Gates and A. Dhuna, "Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation," *Neurology*, vol. 41, pp. 697-702, May, 1991.

[6] H. R.Siebner, C. Rossmeier, C. Mentschel, A. Penemann and B. Conrad, "Short-term motor improvement after sub-threshold 5-Hz repetitive transcranial magnetic stimulation of the primary motor hand area in parkinson's disease," *J. Neurological Sciences*, vol. 178, pp. 91-94, 2000.

[7] G. Hasey, "Transcranial Magnetic Stimulation in the Treatment of Mood Disorder: A Review and Comparison with Electroconvulsive Therapy," *Can J Psy chiatry*, vol. 46, pp. 720-727, Oct., 2001.

[8] A. Pascual-Leone, V. Walsh, and J. Rothwell, "Transcranial magnetic stimulation in cognitive neurosciencevirtual lesion, chronometry, and functional connectivity," *Current Opinions in Neurobiology*, vol. 10, pp. 232-237, 2000.

[9] M. Hamada, R. Hanajima, Y. Terao, N. Arai, T. Furubayashi, S. Inomata-Terada, A. Yugeta, H. Matsumoto, Y. Shirota and Y. Ugawa, "Quadro-pluse stimulation is more effective than paired-pulse stimulation for plasticity induction of the human motor cortex," *Clinical neurophysiology*, vol. 118, pp. 2672-2682, 2007.

[10] G. W. Thickbroom, M. L. Byrnes, D. J. Edwards and F. L. Mastaglia, "Repetitive paired-pulse TMS at I-wave periodicity markedly increases corticospinal excitability: A new technique for modulating synaptic plasticity," *Clinical neurophysiology*, vol.117, pp. 61-66, 2006.

[11] K. Iramina, T. Maeno, Y. Kowatari and S. Ueno "Effects of Transcranial Magnetic Stimulation on EEG Activity," *IEEE Trans. Magn*, vol. 38, pp. 3347-3349, 2002.

[12] K. Iramina, T. Maeno, Y. Nonaka and S. Ueno "Measurement of evoked EEG induced by transcranial magnetic stimulation," *J. Appl. Phys*, vol. 93, pp. 6718-6720, 2003.

[13] T. Paus, P. K. Sipila and A. P. Strafella "Synchronization of neuronal activity in the human primary cortex by transcranial magnetic stimulation: an EEG study," *J Neurophysiol*, vol. 86, pp. 1983-1990, 2001.

[14] G. Thut, J. R. Ives, F. Kampmann, M. A. Pastor, and A. Pascual-Leone, "A new device and protocol for combining TMS and online recordings of EEG and evoked potentials," *J Neurosci. Methods*, vol. 15, p. 141, Feb., 2005.

[15] T. Torii, A. Sato, Y. Masada, Y. Nakahara, M. Iwahashi and K. Iramina, "Effect of the Short-Term Magnetic Stimulation by rTMS on P300 latencies," *The 2011 Biomedical Engineering International Conference Proceeding*, pp. 7-10, 2011.

[16] M. Iwahashi, Y. Katayama, S. Ueno and K. Iramina "Effect of Transcranial magnetic stimulation on P300 event-related potential," *IEEE EMBS 31th*, pp. 1359-1362, Sep. 2009.

[17] N. R. Cooper, P. B. Fitzgerald, R. J. Croft, D. J. Upton, R. A. Segrave, Z. J. Daskalakis and J. Kulkarni, "Effects of rTMS on an auditory oddball task: a pilot study of cortical plasticity and the EEG," *Clinical EEG and neurosocience*, vol. 39, pp. 139-143, 2008.

[18] E. M. Wassermann, "Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guideline from the international Workshop on the safety of Repetitive Transcranial Magnetic Stimulation," *Electroencephalography and Clinical Neurophysiology*, vol. 106, pp.156–164, June, 1996.

[19] R. Chen, J. Classen, C. Gerolff, P. Celnik, E. M. Wassermann, M. Hzllett, L. G. Cohen, "Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation," *Neurology*, vol. 48, pp. 1398-1403, May, 1997.

[20] A. Berardelli, M. Inghilleri, J.C. Rothwell, S. Romeo, A. Currà, F. Gilio, N. Modugno and M. Manfredi, "Facilitation of muscle evoked responses after repetitive cortical stimulation in man," *Exp Brain Res*, vol. 122, pp.79-84, 1998.

[21] E. Halgren, K. Marinkovic, P. Chauvel, "Generators of the late cognitive potentials in auditory and visual oddball tasks," *Electroencephalography and Clinical Neurophysiology*, vol. 106, pp.156–164, 1998.

[22] D. Knoch, P. Brugger and M. Regard, "Suppressing versus releasing a habit: Frequency-dependent effects of prefrontal transcranial magnetic stimulation," *Cerebral Cortex*, vol. 15, pp. 885-887, 2005.

[23] Y. Mano, Y. Morita, R. Tamura, S. Morimoto, T. Takayanagi and R. F. Mayer, "The site of action of magnetic stimulation of human motor cortex in a patient with motor neuron disease," *J Electromyography Kinesiology*, vol. 3, pp.245-250, 1994.

[24] Y. Mano, T. Nakamurro, K. Ikoma, T. Takayanagi and R. F. Mayer, "A clinicophysiologic study of central and peripheral motor conduction in hereditary demyelinating motor and sensory neuropathy," *Electromyogr. Clin. Neurophysiol.*, vol. 33, pp. 101-107, 1993.