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The Impact of rTMS over the Dorsolateral Prefrontal Cortex on Cognitive Processing

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Abstract— **The purpose of the present study was to use event-related potentials (ERP) to clarify the effect of magnetic stimulation on cognitive processing. A figure eight-shaped flat repetitive transcranial magnetic stimulation (rTMS) coil was used to stimulate either the region over the left or the right dorsolateral prefrontal cortex, which is considered to be the origin of the P300 component. Stimulus frequencies were 1.00, 0.75 and 0.50 Hz rTMS. The strength of the magnetic stimulation was set at 80% of the motor threshold for each participant. The auditory oddball task was used to elicit P300s before and shortly after rTMS, and comprised a sequence of sounds containing standard (1 kHz pure tone, 80% of trials) and deviant (2 kHz pure tone, 20% of trials) stimuli. We found that a 1.00 Hz rTMS pulse train over the left dorsolateral prefrontal cortex increased P300 latencies by 8.50 ms at Fz, 12.85 ms at Cz, and 11.25 ms at Pz. In contrast, neither 0.75 and 0.50 Hz rTMS pulse trains over the left dorsolateral prefrontal cortex nor 1.00, 0.75 and 0.50 Hz rTMS pulse trains over the right dorsolateral prefrontal cortex altered P300 latencies. These results indicate that rTMS frequency affects cognitive processing. Thus, we suggest that the effects of rTMS vary according to the activity of excitatory and inhibitory neurons in the cerebral cortex.**

I. Introduction

Barker et al. described a noninvasive method of directly stimulating the human motor cortex using a pulsed magnetic field [1]. Using repetitive transcranial magnetic stimulation (rTMS), one is able to noninvasively induce both facilitation and inhibition in the cerebral cortex. The effects of rTMS may depend on the stimulus frequency, intensity, duration or interval of the stimulation. Fast or high-frequency rTMS refers to rTMS with a stimulus rate of greater than 1 Hz, while slow or low-frequency rTMS refers to rTMS with a stimulus rate of less than 1 Hz [2]. The modulating effects of rTMS on cortical excitability can be facilitatory or inhibitory, as follows: low-frequency rTMS (1 Hz or less) has been found to decrease cortical excitability, while high-frequency rTMS (more than 5Hz) has been found to increase excitability [3-5]. While some studies have used MEPs (motor evoked potentials) to assess the effects of TMS and rTMS, others have focused on ERPs (event-related potentials) [6-9]. When TMS and rTMS are combined with EEG analysis, EEG has a suitable temporal resolution for studying transient neuronal responses [10]. Such studies have indicated that the effect of rTMS is dependent on the specific stimulation point targeted [6-8]. However, to our knowledge, no studies have explored the effects of frequency-dependent rTMS on ERPs. Low-frequency rTMS over the frontal cortex has been suggested as a safer and more tolerable alternative to high-frequency rTMS for the treatment of major depressive disorder [11]. Choosing low-frequency over high-frequency rTMS may also minimize the risk of adverse events, such as seizures [2]. Many studies have reportedly used a minimum stimulation intensity of 80% MT (motor threshold) and a maximum stimulation intensity of 120 % MT [12]. In addition, rTMS studies often make use of long-term pulse trains. The effects of rTMS pulses are cumulative in the brain and summation increases the likelihood of seizure induction [13-15].

More information is needed about the influence of TMS and rTMS parameters (e.g. frequency, intensity, and stimulation site), mechanisms, and the resulting effect on plasticity of brain function [10]. Therefore, we chose to investigate the effects of low-frequency, sub-threshold rTMS with a short pulse train, in order to elucidate the effects of low-frequency rTMS. The latency of the P300 ERP component was used to evaluate the effects of low-frequency rTMS. We used stimulus frequencies of 1.00, 0.75, and 0.50 Hz with short pulse trains and sub-threshold intensities (i.e., 100 pulses at 80% MT). Previous studies have found that low-frequency rTMS decreases cortical excitability, whereas high-frequency rTMS increases cortical excitability [2–4]. Accordingly, we hypothesized that low-frequency (1.00, 0.75, and 0.50 Hz) rTMS would delay P300 latencies.

II. Methods

A. Participants and experimental procedure

Our participants comprised 20 healthy right-handed volunteers who all gave informed consent. The participants ranged in age from 23-38 years: eleven males and nine females with a mean age 31.2 years (SD = 7.0). None of the

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participants had a history of neurological or psychological disorders. All participants were instructed to relax and remain seated during testing.

The experimental procedure was as follows: first, a baseline P300 latency was measured using the auditory oddball task. Second, a rTMS pulse train (100 magnetic pulses) was applied over either the left or the right dorsolateral prefrontal cortex (DLPFC) at an intensity of 1.00, 0.75, or 0.50 Hz. Immediately afterwards, the latency of the P300 ERP component was again measured using the auditory oddball task.

B. Measurement of event-related potentials

The ERP measurements were conducted using STIM2 software (Compumedics Neuroscan USA Ltd, North Carolina, USA) to output the pure tones and trigger signal. The pure tones were used to induce the P300 ERP component in the auditory oddball task. The trigger signal was used to mark the start of the ERP measurements. ERPs were measured from the Fz, Cz and Pz electrodes, according to the international 10-20 electrode system. Electrode impedances were less than 5k ohm. ERP data were measured for 1,000 ms from the onset of the trigger or stimulation sound in the auditory oddball task. Recording began with the standing edge of the stimulation sound. The sampling frequency was 1,000 Hz and the data were averaged 20 times. Recorded data were processed using a band-pass digital filter from 0.5-50 Hz.

The auditory oddball task was presented as a sequence of sounds containing non-target (1 kHz pure tone) and target (2 kHz pure tone) stimuli. The non-target stimulus was presented in 80% of the pulse trains. The target stimulus was presented in 20% of pulse trains. The auditory stimuli were presented in a random order, and each pulse consisted of a burst wave with a duration of 50 ms. The interval between the auditory pulse trains was 2,500 ms and the stimulus pressure was 60 dB. Participants were instructed to click a button on a computer mouse when they detected the target stimuli in the auditory oddball task.

C. Magnetic stimulation

A Super Rapid Stimulator (Magstim Co. Ltd, Carmarthenshire, UK) with a figure eight-shaped flat coil (70 mm diameter) was used as the magnetic stimulating device. rTMS was conducted with stimulation frequencies of 1.00, 0.75, and 0.50 Hz over either the left or right DLPFC. As mentioned above, this region was used because is it considered to be the origin of the P300 signal [16]. In addition, rTMS over the DLPFC is used to treat depression. rTMS consisted of 100 magnetic pulses, each with a width of 2 ms. The magnetic stimulation intensity was set 80% of the resting motor threshold for each participant. The point at which MEPs with a peak-to peak amplitude greater than 50 μV were obtained in at least 5 of 10 successive trials was used as the individual motor threshold.

D. ERP data statistical analysis

The P300 component was measured by assessing latency (timing). Latency (ms) is defined as the time from stimulus onset to the point of maximum positive amplitude within the latency window [17]. In this study, the positive peak of the ERP in the 250-400 ms range was taken as a P300. Wilcoxon signed-rank tests were used to compare P300 latencies pre- and post-rTMS.

III. RESULTS

We found that the post-rTMS P300 latency over the left DLPFC varied according to the frequency of the rTMS (Figure 1). For instance, application of a 1.00 Hz rTMS pulse train over the left DLPFC produced an increased P300 latency compared with the control condition. On average, a 1.00 Hz rTMS pulse train over the left DLPFC increased P300 latencies by 8.50 ms at the Fz electrode, 12.85 ms at the Cz electrode, and 11.25 ms at the Pz electrode. In contrast, the application of a 0.75 Hz rTMS pulse train over the left DLPFC produced only a minor change in the P300 latencies compared with the control condition. On average, a 0.75 Hz rTMS pulse train over the left DLPFC altered P300 latencies by 2.80 ms at the Fz electrode, 0.10 ms at the Cz electrode, and 4.00 ms at the Pz electrode. The application of a 0.50 Hz rTMS pulse train over the left DLPFC also produced only a minor change in the P300 latencies compared with the control condition. On average, a 0.50 Hz rTMS pulse train over the left DLPFC altered P300 latencies by 1.10 ms at the Fz electrode, 4.90 ms at the Cz electrode, and 6.55 ms at the Pz electrode. rTMS over the right DLPFC produced only minor changes in P300 latency relative to the frequency of rTMS. Specifically, the application of a 1.00 Hz rTMS pulse train over the right DLPFC had a minimal effect on P300 latencies compared with the control condition. On average, a 1.00 Hz rTMS pulse train over the right DLPFC altered P300 latencies by 0.55 ms at the Fz electrode, 0.35 ms at the Cz electrode, and 4.15 ms at the Pz electrode. The application of a 0.75 Hz rTMS pulse train over the right DLPFC produced only a minor change in the P300 latencies compared with the control condition. On average, a 0.75 Hz rTMS pulse train over the right DLPFC altered P300 latencies by 4.35 ms at the Fz electrode, 2.20 ms at the Cz electrode, and 0.35 ms at the Pz electrode. Finally,

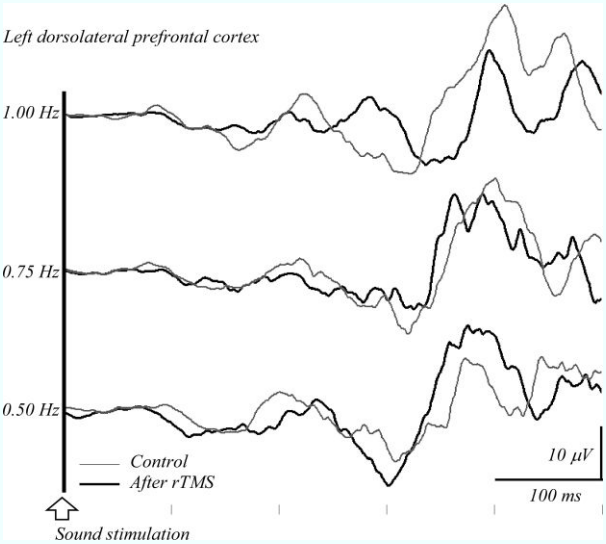

Figure 1. ERPs at the Fz electrode before and after 1.00, 0.75, and 0.50 Hz rTMS over the left DLPFC.

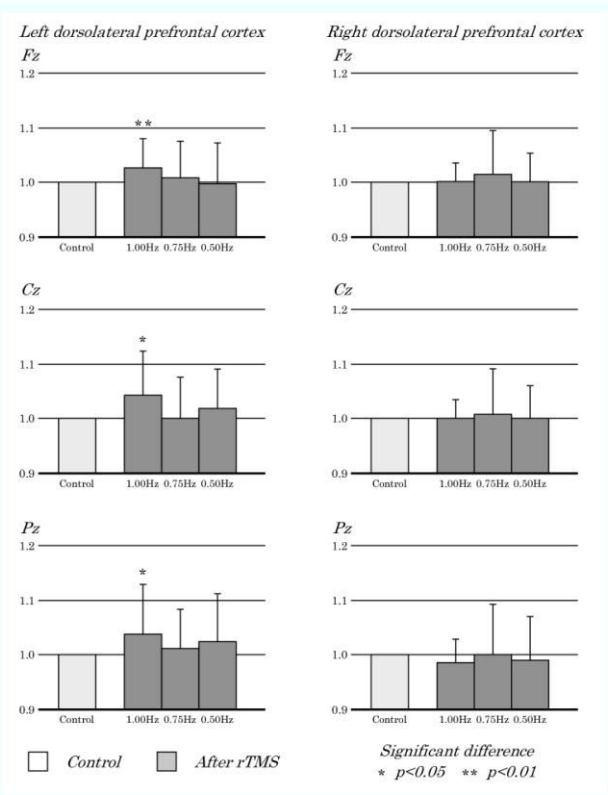

Figure 2. Normalized P300 latencies at the Fz (top), Cz (middle), and Pz (bottom) electrodes before and after stimulation of the left or right DLPFC.

the application of a 0.50 Hz rTMS pulse train over the right DLPFC had little effect on P300 latencies compared with the control condition. On average, a 0.50 Hz rTMS pulse train over the right DLPFC altered P300 latencies by 0.60 ms at the Fz electrode, 0.35 ms at the Cz electrode, and 2.65 ms at the Pz electrode.

We normalized the P300 latency using each control condition. Wilcoxon signed-rank test was used to examine whether there were significant differences in the normalized P300 latency before vs. after rTMS (Figure 2). The application of a 1.00 Hz rTMS pulse train over the left DLPFC significantly increased the P300 latency after the magnetic stimulation in comparison with the control condition. This increase was significant by $p<0.01$ at the Fz electrode, $p<0.05$ at the Cz electrode, and $p<0.05$ at the Pz electrode. Conversely, the application of a 0.50, or 0.75 Hz rTMS pulse train over the left DLPFC did not have a significant effect on the P300 latency after the magnetic stimulation compared with the control condition. In addition, the application of a 0.50, 0.75, or 1.00 Hz rTMS pulse train over the right DLPFC did not have a significant effect on the P300 latency after the magnetic stimulation compared with the control condition.

IV. Discussion

This study used low-frequency rTMS to clarify the effects of frequency and site dependence on the P300 ERP component. Previous studies have reported that low-frequency rTMS decreases cortical excitability (i.e. rTMS at a frequency of less than 1.0 Hz), whereas high-frequency rTMS increases cortical excitability (i.e. rTMS at a frequency of more than 5 Hz) [3-5]. Our findings indicate that low-frequency rTMS, specifically at a frequency of 1.00 Hz, delays P300 latency. These results are consistent with other frequency-dependent effects observed in the left, but not the right DLPFC [7, 18]. The P300 ERP component is thought to reflect neuro-electric activity related to cognitive processes [17]. Previous studies have suggested that P300 activity recorded at the scalp is primarily indicative of cortical processes [19-21], and that the P300 component reflects neural activity that is related to basic aspects of cognition [17]. Fatigue due to sleep deprivation is known to increase P300 latency, and similar effects are produced by sedatives [22-24]. Therefore, it is likely that the P300 is sensitive to the physiological arousal of the cerebral cortex [17]. This study has indicated that the left DLPFC is involved in generating the P300 ERP component. Specifically, it appears that the left DLPFC is more susceptible to magnetic stimulation and is more involved in the generation of the P300 than the right DLPFC. Therefore, we suggest that rTMS affects recognition processing.

Low-frequency rTMS has been successfully used to treat mental disorders (including auditory hallucinations, depression, and epilepsy) [12]. Therefore, rTMS may coordinate activity in the cerebral cortex. However, the mechanism by which rTMS has an effect on the cortex is unclear. Recent studies have suggested that plasticity induced by rTMS includes long-term potentiation-like and long-term depression-like changes in the auditory cortex [25-30]. In addition, it has been suggested that TMS and rTMS might stimulate pyramidal tract neurons [31-33]. TMS and rTMS have been shown to directly induce neuronal activity [34, 35], and as a result they are thought to specifically affect excitatory synapses. Considering these findings, we would like to make the following suggestions: rTMS-induced neuronal activity increases the activity of inhibitory neurons. Subsequently, the excited neurons are inhibited, and this inhibited state gradually returns to the resting state. This inhibition may also be produced by low-frequency rTMS. Our hypothesis was supported by our observations regarding the effect of 1.00 Hz rTMS over the left DLPFC. It is possible that activity in the cerebral cortex was suppressed by a 1.00Hz rTMS pulse train over the left DLPFC. However, we found no increase or decrease in P300 latency after low-frequency magnetic stimulation at 0.75 or 0.50 Hz over the left DLPFC. We also found no change after low-frequency magnetic stimulation at 1.00, 0.75 or 0.50 Hz over the right DLPFC. It is possible that rTMS at 1.00, 0.75 and 0.50 Hz over the right DLPFC and 0.75 and 0.50 Hz over the left DLPFC caused the excited cerebral cortex to shift to a resting condition. Given the relationship between neuronal condition and P300 latency, it appears that neuronal activation can lead to an increase or decrease in P300 latency. Therefore, a decrease in neuronal excitation (i.e. excitation of the cerebral cortex) may cause the observed increase in P300 latency. The conditions with no alteration of the P300 latency are regarded as the conditions in which the above-mentioned biochemical reaction had been completed.

V. Conclusion

The purpose of this study was to clarify the effects of low-frequency rTMS on human brain activity. We used the latency of the P300 ERP component to evaluate the effects of low-frequency rTMS by stimulating the bilateral DLPFC. We applied rTMS at frequencies of 1.00, 0.75 and 0.50 Hz, although significant effects were observed only after 1.00 Hz rTMS over the left DLPFC. Therefore, we suggest that the effects of rTMS over the left DLPFC on P300 latency are frequency-dependent. In contrast, rTMS over the right DLPFC had no effect on P300 latency. This study indicates that the effects of rTMS are dependent on stimulation frequency and stimulation site. In addition, we suggest that rTMS affects recognition process.

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