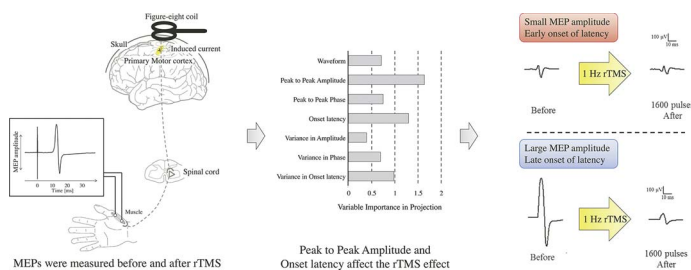


Research paper

Relationship between rTMS effects and MEP features before rTMS

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GRAPHICAL ABSTRACT



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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a promising method for use in the clinical field, as it can induce modulation of cortical excitability. Generally, rTMS inhibits the motor cortex when delivered at less than 1 Hz. However, it has been indicated that a facilitative effect is induced by 1 Hz rTMS, depending on the stimulation parameters and the individual. Therefore, the aim of this study was to investigate the features of the subject that could affect the 1 Hz rTMS effect when rTMS stimulus conditions change.

First, motor evoked potentials (MEP) were measured under rTMS conditions with a variety of stimulus intensities and numbers of pulses. The MEP features before rTMS and the MEP modulation by the rTMS were then analyzed. Furthermore, correlations between the MEP features and the rTMS effect were investigated. It was found that the MEP amplitude and MEP onset before rTMS can influence the rTMS effect. Furthermore, negative correlations were found between these MEP features and the rTMS effect. MEPs with a small amplitude and early latency were little influenced by the inhibitive effect of 1 Hz rTMS, while MEPs with a large amplitude and late latency were readily affected by the inhibitive effect of 1 Hz rTMS. In this study, we focused on the MEP features before rTMS and identified the features of the subject that could influence the rTMS effect when the rTMS stimulus condition was changed.

1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive and painless method of stimulating neurons through the electromagnetic induction of current in the brain. Repetitive TMS (rTMS) is a stimulation method that applies successive TMS pulses. rTMS can either inhibit or facilitate neuronal activity in the brain, and it has therefore been used in the study of a variety of brain functions, such as motor control,

memory, attention, and cognitive and visual perception [1], as well as for the clinical treatment of diseases including stroke, depression, Parkinson's disease, chronic pain, dystonia, and epilepsy [2,3].

When TMS is applied over a subject's motor cortex, corticospinal neurons may be activated, eliciting a descending volley to targeted muscles. This activation elicits a muscle response referred to as a motor evoked potential (MEP). The size of the resulting MEP reflects cortical excitability, whether rTMS induces excitation or inhibition, and

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therefore, rTMS effects can be quantified by the size of MEPs. Generally, rTMS inhibits the motor cortex when delivered at less than 1 Hz [4] and excites it when delivered at over 5 Hz [5]. Additionally, the rTMS intensity and the number of pulses can affect brain activity [6,7]. Maeda et al. showed that the rTMS effect of 1600 rTMS pulses was stronger than that of 240 rTMS pulses [6]. Using 900 pulses at 1 Hz, Fitzgerald et al. applied rTMS (85% or 115% resting motor threshold (RMT)). rTMS (Both 85% and 115% RMT) increased the RMT, but only rTMS (115% RMT) decreased the MEP amplitude [7]. However, it has been indicated that MEPs are increased by the use of 1 Hz rTMS, depending on the stimulation parameters [4,8] and the individual [9]. Therefore, the aim of this study was to investigate the features of the subject that could influence the 1 Hz rTMS effect when the rTMS stimulus condition is changed.

2. Material and methods

MEPs were measured before and after applying rTMS, with the rTMS being applied at various intensities and pulse numbers. The MEP modulations and the pre-rTMS MEP data were then subjected to partial least squares (PLS) regression analysis to investigate the MEP features influencing the rTMS effect. Furthermore, correlations between the MEP features and MEP modulations were analyzed.

2.1. Subjects

Sixteen healthy right-handed subjects (13 males, 3 females; aged 22–38 years) were enrolled in the experiments. As 2 subjects were assessed twice and 1 subject was assessed three times, the total number of assessments was 20. Before the experiments, the subjects were informed of the aim of the study, the study procedures, the potential hazards of the stimulation, and the data management procedures. All subjects gave their written consent before participating and the study protocol was approved by the Kyushu University ethics committee.

2.2. Materials and stimuli

Electromyograms (EMGs) were recorded from electrodes placed over the abductor pollicis brevis (APB) muscle of the right hand, with a circular ground electrode placed over the wrist. EMG signals during the MEPs were measured at a sampling rate of 10240 Hz and filtered with a 5–3000 Hz band-pass filter. The MEP base line was confirmed to be free of noise. EMGs were recorded using a NeuropackX1 (Nihon Kohden, Tokyo, Japan). When the MEP was measured, 120% RMT TMS was applied ten times with a stimulus interval of 4 s. RMT was defined as the minimum stimulation intensity to evoke an MEP greater than 50 μ V in at least 5 of 10 single-pulse TMS trials applied to the left primary motor cortex (M1). rTMS was delivered using a Magstim Super Rapid Stimulator (Magstim Comp., Whitland, UK) and a 70 mm figure-of-eight coil, which was air-cooled to attenuate coil overheating from the vacuum unit. The coil did not need to be replaced during the experiment. The head of the subject was fixed with a cheek-rest and the rTMS coil was held with an arm stand. The same region of stimulation was therefore maintained throughout the experiment. The current waveform was biphasic and the coil was angled 45° from the midline with the handle pointing backwards. The direction of induced current was set posterior to anterior. The point of stimulation was confirmed by magnetic resonance imaging and a neuronavigation system (Brain Sight, Rogue Research Inc., Montreal, Canada).

rTMS was then systematically applied over the left M1 and MEPs were measured, as shown in Fig. 1(a). Fig. 1(b) shows the time scale of the experiment. MEPs were measured before rTMS (baseline) and after delivery of every 200 rTMS pulses. The frequency of the rTMS was fixed at 1 Hz, as this frequency is generally used more often than other low frequencies, and the inhibitory effect is reported to be more apparent at 1 Hz than at other frequencies [10]. A total of 1800 pulses were applied

at 85%, 100%, or 115% of RMT over a period of approximately 40 min. It has been reported that the effects of rTMS differ between super-threshold and sub-threshold stimulation [7], which is the reason why stimulus intensities of 85%, 100%, and 115% RMT were used. An MEP measurement of approximately 1 min (about 20 s for setting the stimulus intensity and interval of TMS, and then 40 s for applying TMS 10 times every 4 s) was made between each train of 200 pulses. Each of the conditions (85%, 100%, or 115% RMT) was performed on different days, separated by at least 1 week. All experiments were performed during the daytime.

The MEP amplitudes were calculated to investigate how they were modulated by the rTMS parameters. First, the stimulation data that did not evoke MEPs were excluded from the analysis (8.98% of all the data). The remaining data were then averaged and the peak-to-peak amplitudes of the MEPs before and after the rTMS were calculated. MEP modulation was calculated using formula (1).

$$MEP\ modulation[\%] = \frac{MEP_{After\ rTMS[\mu V]} - MEP_{Before\ rTMS[\mu V]}}{MEP_{Before\ rTMS[\mu V]}} \quad (1)$$

Data analysis was performed using MATLAB (R2007b, The Math Works Inc., Natick, MA, USA).

2.3. PLS regression analysis

PLS regression analysis is a method to investigate the relationship between independent variables and a dependent variable [11]. Variable importance in projection is obtained by the method of covariance calculation for each independent variable and any interaction terms, which indicate how much they influence the dependent variable.

When the neurons in the cortex are stimulated by TMS, descending volleys with different phases are induced. These descending volleys are called I1, I2, and I3 (indirect wave: I-wave), in order from early to late phase, because they are induced by the indirect stimulation of pyramidal neurons [12]. These I-waves elicit the MEP. A previous study demonstrated that the rTMS effect can be rated according to whether I-waves were readily recruited [13]. Therefore, we focused on the features of the MEP before rTMS in this study. The analyzed data of the MEP modulations were the independent variables, and the MEP features before the rTMS were the dependent variables.

The analyzed data of the MEP modulations (calculated using formula (1) after 200–1800 rTMS pulses) at each stimulus intensity were used. MEP modulations were calculated for every subject (20 assessments), for every stimulus pulse (9 conditions), and at each stimulus intensity (3 conditions). Thus, the MEP modulation data consisted of 180 data points (20 assessments $\times$ 9 conditions) for each of the three stimulus intensities (85%, 100%, and 115% RMT).

Seven features of the MEPs occurring before rTMS were used: 1) the waveform (whether it was biphasic or not); 2) the peak-to-peak amplitude; 3) the peak-to-peak phase (the interval between the peak points); 4) the onset latency (the time of onset of the MEP); 5) the variance of the amplitude; 6) the variance of the phase; and 7) the variance of the onset latency. Thus, the MEP feature data before rTMS consisted of 140 data points (20 assessments $\times$ 7 features) for each of the three stimulus intensities (85%, 100%, and 115% RMT).

Furthermore, correlations between the MEP features and MEP modulations were analyzed using Spearman's correlation coefficients.

3. Results

Fig. 2(a) shows the result of the PLS regression analysis. Variable importance in projection of the MEP features before rTMS are shown. The peak to peak amplitude and onset latency of the MEP were found to influence the rTMS effect. Fig. 2(b) shows examples of the MEP waveforms after applying 85% RMT rTMS.

According to these results, we analyzed the correlation between the

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