35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Predicting rTMS Effect for Deciding Stimulation Parameters

K. Nojima, Y. Katayama and K. Iramina, *Member, IEEE*

Abstract— **Repetitive transcranial magnetic stimulation (rTMS) is used in the medical field to modulate cortical excitability. However, when applied in this setting, rTMS stimulation parameters are not usually decided objectively. The aim of this study is to make a model that predicts the rTMS effect, allowing stimulation parameters (intensity and pulse number) to be easily determined before use. First, we investigated the relationship between stimulation condition and rTMS outcome. rTMS delivered at 1 Hz was applied with stimulation intensities of 85%, 100%, or 115% resting motor threshold (RMT) over the primary motor cortex in the left hemisphere. Motor-evoked potentials (MEPs) were measured before rTMS and after every 200 rTMS pulses. Eighteen hundred pulses were applied for each stimulation condition. Results showed that more pulses and stronger intensities lead to a larger decrease in MEP amplitude. An initial prediction model was then made by applying multiple regression analysis over the experimental data. We then adjusted the model depending on the size of the initial MEP amplitude before rTMS, and confirmed the improvement.**

I. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive and painless method to stimulate neurons through electromagnetic induction of current in the brain. Repetitive TMS (rTMS) is a stimulation method that applies TMS in succession. rTMS is used in the medical field to both inhibit or facilitate neuronal activity in the brain. When TMS is applied over a subject's motor cortex, corticospinal neurons are activated, eliciting a descending volley to targeted muscles. This elicits a muscle response referred to as a motor evoked potential (MEP). Whether rTMS is excitatory or inhibitory is determined by the size of the MEP [1]. Generally, motor cortex is inhibited by rTMS of less than 1 Hz [2] and excited by that over 5 Hz [3]. Additionally, rTMS-stimulus intensity and the number of pulses also affect brain activity [4], [5]. A cortical mechanism involving a process analogous to long-term synaptic depression or long-term potentiation is theorized to produce these effects [6].

Medically, rTMS is used in the treatment of depression [7], stroke [8], chronic pain [9], Parkinson's disease [3] and dystonia [10]. When treating depression, rTMS is used to excite the left prefrontal area to combat the inhibition observed in depression [7]. When treating stroke, the primary motor cortex (M1) of the undamaged hemisphere is inhibited, or that of the lesioned hemisphere is facilitated to restore balance. This is because normally each M1 inhibits the other. When one is damaged, balance is disrupted, and the M1 of undamaged hemisphere exerts unchecked inhibition on the lesioned hemisphere [8].

rTMS has therefore drawn attention as a promising treatment method. However, rTMS stimulation parameters (intensity and pulse number) have not been quantitatively determined. The aim of this study is to make a prediction model of rTMS effects on MEPs so that stimulation parameters can be easily determined before use. For the first step, we investigated the relationship between stimulation parameters and the effects of rTMS. We made the prediction model using multiple regression analysis.

II. Materials And Methods

To investigate the relationship between stimulation parameters and the effects on MEP, rTMS was systematically applied over left-hemisphere M1, and MEPs were measured.

Ten healthy, right-handed subjects (8 males, 2 females; ages 22–32 years) participated in this experiment. Before the experiment, they were introduced the aim of the study, the procedures and hazards of the stimulation, and the data management. All subjects gave their written consent before participating.

Fig. 1 shows the time sequence of the experiment. MEPs were measured before rTMS (baseline) and after every 200 pulses delivered at 1 Hz. Eighteen hundred rTMS pulses were applied at 85%, 100%, or 115% resting motor threshold (RMT). Each condition was performed on a separate day, and experiments were separated by more than one week. These stimulation parameters adhered to rTMS safety guidelines [11]. rTMS was delivered using a Magstim Super Rapid Stimulator (Magstim Comp., Whitland, UK) using a figure-eight 70-mm coil, and an air-cooled coil to attenuate coil over-heating from the vacuum unit. The coil did not need replacing during the experiment. The point of stimulation was confirmed by magnetic resonance imaging and an infrared camera (Brain Sight, Rogue Research Inc., Montreal, Canada). The 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 backward. The direction of induced current was set posterior to anterior. To estimate the RMT, we applied TMS over the motor area in the left hemisphere and recorded the MEPs. The RMT was defined as the minimal stimulation intensity that evoked an MEP greater than 50 μV in at least 5 out of 10 single-pulse TMS.

Kazuhisa Nojima is with the Graduate School of Systems Life Sciences, Kyushu University, 744 Motooka Nishi-ku, Fukuoka, 819-0395, Japan (phone: +81-92-802-3767, e-mail: nojima@bie.inf.kyusyu-u.ac.jp)

Yoshinori Katayama is with the Graduate School of Information Science and Electrical Engineering, Kyushu University, 744 Motooka Nishi-ku, Fukuoka, 819-0395, Japan (email: yosinori@inf.kyushu-u.ac.jp)

Keiji Iramina is with the Graduate School of Systems Life Sciences and the Graduate School of Information Science and Electrical Engineering, Kyushu University, 744 Motooka Nishi-ku, Fukuoka, 819-0395, Japan (phone & fax: +81-92-802-3581, e-mail: iramina@inf.kyushu-u.ac.jp).

978-1-4577-0216-7/13/$26.00 ©2013 IEEE

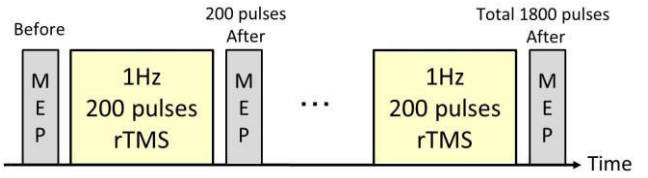

Fig.1 Time sequence of this experiment
MEPs were measured before rTMS and after every 200 pulses. Eighteen hundred pulses were applied for each rTMS condition (85%, 100%, or 115% RMT).

MEPs were recorded from electrodes placed over the contralateral (right) abductor pollicis brevis (APB) muscle in the hand, and a circular ground electrode was placed over the subjects' wrists. The EMG signals were filtered with a 5–3000 Hz band-pass filter during MEP measurement at a sampling rate of 20,480 Hz.

III. Analysis And Results

To investigate the modulation of MEP amplitude depending on rTMS condition, peak-to-peak amplitudes of MEPs were calculated. The main value for the analysis was the calculated difference in MEP amplitude between pre- and post-rTMS. First, peak-to-peak amplitudes of 10 MEPs were calculated. Then, amplitudes over 20 μV were analyzed and data more than twice the standard deviation from the mean were removed as outliers. This time 4.48% of data was removed by this process. Finally, we averaged the remaining data and calculated the peak-to-peak amplitude of the MEP. Data analysis was performed using MATLAB (R2007b, The MathWorks Inc., Massachusetts, USA).

Fig. 2 presents the results of MEP-amplitude modulation. Result showed that both stronger intensities and higher numbers of pulses led to a greater decrease in MEP amplitude. Especially, rTMS with 85% RMT induced the largest decrease in MEP.

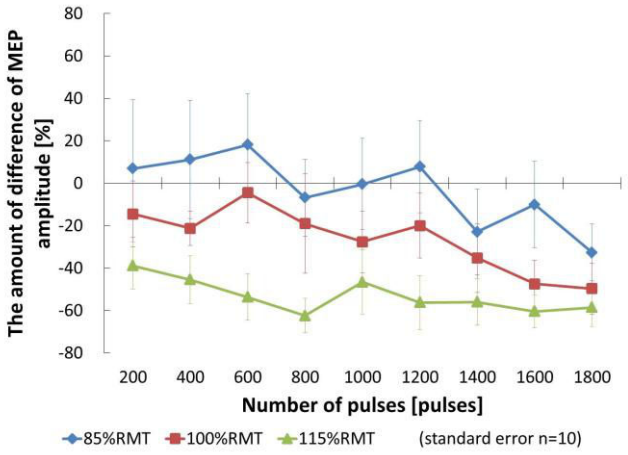

Fig. 2 Modulation of MEP amplitude
Results showed that rTMS with 85% RMT induced the largest decrease in MEP. In all the conditions, stronger intensities and more pulses led to greater MEP-amplitude decreases.

IV. The Prediction Model

By using these experimental results, we made a prediction model of rTMS effects on MEPs. First, we investigated the interaction between stimulation intensity and number of pulses. Fig. 3 shows the model tree for MEP amplitude difference. Results showed that stimulation intensity is the most important factor that affects MEP amplitude. When the intensity is over 107.5% RMT, MEP amplitudes differ by about -53%. When intensity is under 107.5% RMT, the number of pulses has a greater effect on MEP amplitude. When pulse number is over 1300, MEP-amplitude difference is about -32%. When it is under 1300, intensity plays a more important role in affecting the MEP amplitude. An interaction between stimulus intensity and the number of pulses is therefore likely.

We made the prediction model from these experimental data and the results from the model tree. The general model is represented in (1), where Y is the amount of MEP-amplitude difference, X_1 is stimulation intensity, and X_2 is number of pulses.

$$Y = f(X_1, X_2) \quad (1)$$

Y: the amount of difference in MEP amplitude,
X_1: stimulus intensity, X_2: pulse number

The initial model was made from the relationship between the rTMS condition and the amount of MEP-amplitude difference (2). We added the square of X_1 and X_2 and the product of X_1 and X_2. Because the relationship is not linear and perhaps X_1 and X_2 have an interaction.

$$Y = \beta_1 * X_1 + \beta_2 * X_2 + \beta_3 * X1^2 + \beta_4 * X_2^2 + \beta_5 * X_1 * X_2 + \beta_6 \quad (2)$$

Coefficients: $\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6$

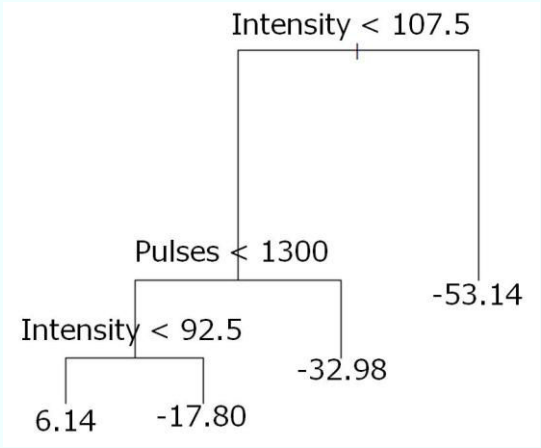

Fig.3 Model tree on the amount of difference of MEP amplitude
It was found that stimulus intensity is the most important condition which affects the MEP amplitude. When the intensity is over 107.5% RMT, the amount of difference on MEP amplitude is about -53%. While it is under 107.5% RMT, instead of the intensity, the number of pulses mainly affects the MEP amplitude. There is a potential for an interaction between stimulus intensity and the number of pulses.

To determine the coefficients of (2), a stepwise multiple linear regression analysis was applied. The results can be seen in model A (3). The coefficient of determination for the model was 0.883. This means that this model can predict Y in 88.3% with X_1, and X_2. Table 1 (a) shows measured and predicted values using model A. Large prediction errors were observed using model A if the initial MEP amplitude before stimulation was extreme.

$$\text{Model A: } Y = -0.008*X_1^2 - 9.626*10^{-6}*X_2^2 + 69.037 \quad (3)$$
$$\{85 \le X_1 \le 115,\ 200 \le X_2 \le 1800\}$$
$$R^2 = 0.883\ (F = 99.078,\ p < 0.001)$$

Therefore, we adjusted the model to take the MEP amplitude before rTMS into account. Model B (4) was made for small initial MEPs using data in which peak-to-peak MEP amplitude before rTMS was under 500 μV. Model C (5) was made for large initial MEPs using data in which peak-to-peak MEP amplitude before rTMS was over 200 μV.

Then, depending on the initial MEP amplitude, model A, B, or C was applied to the data. Model B was applied to MEP data with pre-rTMS peak-to-peak amplitudes of 20–200 μV, Model A for amplitudes of 200–500 μV, and Model C for those over 500 μV. Table 1 (b) shows that these adjusted models effectively reduced the prediction error.

$$\text{Model B: } Y = -0.013*X_1^2 - 1.151*10^{-5}*X_2^2 + 125.057 \quad (4)$$
$$\{85 \le X_1 \le 115,\ 200 \le X_2 \le 1800\}$$
$$R^2 = 0.923\ (F = 157.511,\ p < 0.001)$$

$$\text{Model C: } Y = -0.007*X_1^2 - 7.932*10^{-6}*X_2^2 + 43.186 \quad (5)$$
$$\{85 \le X_1 \le 115,\ 200 \le X_2 \le 1800\}$$
$$R^2 = 0.709\ (F = 32.605,\ p < 0.001)$$

The equations of (3), (4), (5) were similar. Therefore the variable of the MEP amplitude before rTMS was added. The model is represented in (6).

$$Y = f(X_1, X_2, X_3)$$
$$=\beta_1*X_1+\beta_2*X_2+\beta_3*X1^2+\beta_4*X_2^2+\beta_5*X_1*X_2+\beta_6*X_3+\beta_7 \quad (6)$$

Coefficients: $\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7$, Y: the amount of difference in MEP amplitude, X_1: stimulus intensity, X_2: pulse number, X_3: MEP amplitude before rTMS

To determine the coefficients of (6), a stepwise multiple linear regression analysis was also applied. The results can be seen in model D (7).

Table 1 (c) shows predicted values and prediction error using model D. The results showed this model also reduced the prediction error except the data of large MEP before rTMS.

$$\text{Model D: } Y = -0.009*X_1^2 - 9.690*10^{-6}*X_2^2 - 0.071*X_3 + 99.890 \quad (7)$$
$$\{85 \le X_1 \le 115,\ 200 \le X_2 \le 1800,\ 20 \le X_3 \le 2000\}$$
$$R^2 = 0.836\ (F = 130.008,\ p < 0.001)$$

V. Discussion And Conclusion

Here, we investigated the relationship between rTMS stimulation parameters and their effects on MEP by applying rTMS over left-hemisphere M1 and measuring the change in MEP amplitude. The results showed that stronger intensities or greater numbers of pulses led to larger decreases in amplitude. It is well known the MEP decreases when using 1Hz rTMS. However there are a few contradicting reports that show increased MEP amplitude using 1Hz rTMS depending on the stimulation parameters [12] and the individual [13].

Regarding stimulation intensity, sup-threshold rTMS has been reported to affect cortical neurons more than sub-threshold stimulation [4]. Furthermore, sub-threshold rTMS induces re-afferent feedback activation that is caused by TMS-evoked muscle twitches [14]. This could be why stronger intensity rTMS caused a larger decrease in MEP amplitude.

Regarding pulse number, here we showed that more pulses also caused a larger decrease in MEP amplitude. Maeda et al. reported that 1600 rTMS pulses delivered at 1 Hz decreased MEP amplitude more than 240 pulses did at a stimulus intensity of 90% RMT [13]. Additionally, Touge et al. reported that 1500 rTMS pulses at 1 Hz decreased MEP amplitude more than 150 pulses did at a stimulus intensity of 95% RMT [5]. Our results are consistent with these previous reports.

More importantly, we made a prediction model for the effects of rTMS on MEP by applying a linear regression analysis over experimental data. Before that process, we investigated the interaction between stimulation intensity and number of pulses. The model tree for MEP amplitude difference showed that there is a potential for an interaction between stimulus intensity and the number of pulses. However, the result after applying a linear regression analysis, the model didn't include the variable of interaction (products X_1 and X_2). This means stimulus intensity and the number of pulses are independently. The validity of the model was proved by the high coefficient of determination. However, prediction error was high in the initial model for data in which the initial MEP amplitude was extreme. The next models took initial MEP amplitude into account, and reduced prediction errors are evidence for improvement.

Model B and model C were made for applying the large or small MEP before rTMS. These models decrease the error. However, a prediction error of about 21% still occurred when a small number of rTMS pulses was delivered at low intensity. Furthermore, model D which was adjusted on the initial MEP amplitude was made. This model also decreased the error except the data of large MEP before rTMS.

In the future, we need to improve this prediction model through continued experiments using other stimulation parameters including a stimulus frequency over 5 Hz, which facilitates cortical excitability.

Table.1 Measured and predicted MEP values

(a) Large prediction errors were observed using model A if the MEP amplitude before stimulation was extreme. (b) Depending on the initial MEP amplitude, model A, B, or C was used, and results showed that prediction error decreased. (c) Depending on the initial MEP amplitude, model D was used, and results showed that prediction error decreased except the data of large MEP before rTMS.

Intensity [% RMT]	Pulses [pulses]	MEP before rTMS[μV]	MEP after rTMS[μV]	(a) Model A [μV]		(b) Model A, B or C [μV]		(c) Model D [μV]	
				Predictive	Predictive error	Predictive	Predictive error	Predictive	Predictive error
100	1800	147	59 (-60%)	85 (-42%)	-26 (-18%)	85 (-42%)	-26 (-18%)	100 (-32%)	15 (10%)
115	600	159	54 (-66%)	95 (-40%)	-41 (-26%)	78 (-51%)	-24 (-15%)	105 (-34%)	10 (6%)
85	600	414	360 (-13%)	447 (8%)	-87 (-21%)	447 (8%)	-87 (-21%)	422 (2%)	-25 (-6%)
115	1000	324	149 (-54%)	175 (-46%)	-26 (-8%)	175 (-46%)	-26 (-8%)	156 (-52%)	-19 (-6%)
85	1800	810	482(-41%)	648 (-20%)	-166 (-21%)	543 (-33%)	-61(-7%)	372 (-54%)	-276(-34%)
100	1000	827	523(-37%)	653 (-21%)	-130 (-16%)	538 (-35%)	-15 (-2%)	343 (-59%)	-310 (-38%)

ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research, Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 21300168) and a Grant-in-Aid for JSPS Fellows (24-5413).

REFERENCES

[1] F. Maeda et al. "Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation," *Clin. Neurophysiol.*, vol. 111, pp. 800–805, May, 2000.

[2] R. Chen et al. "Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation," *Neurology*, vol. 48, pp. 1398–1403, May, 1997.

[3] A. Pascual-Leone et al. "Akinesia in Parkinson's disease. II. Effects of subthreshold repetitive transcranial motor cortex stimulation," *Neurology*, vol. 44, no. 5, pp. 892–898, May, 1994.

[4] PB. Fitzgrald et al. "Intensity-dependent effects of 1Hz rTMS on human corticospinal excitability," *Clin Neurophysiol*., vol. 113, pp. 1136–1141, Jul., 2002.

[5] T. Touge et al. "Are the after-effects of low-frequency rTMS on motor cortex excitability due to change in the efficacy of cortical synapses?" *Clin Neurophysiol.*, vol. 112, pp. 2138–2145, Nov., 2001.

[6] S. M. Dudek and M. F. Bear, "Homosynaptic long-term depression in area CAl of hippocampus and effects of N-methyl-D-aspartate receptor blockade," *Neurobiology*, vol. 89, pp. 4363–4367, May, 1992.

[7] M. S. George et al. "Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression," *Neuroreport*, vol. 6, no. 14, pp. 1853–1856, Oct., 1995.

[8] F. C. Hummel and L. G. Cohen, "Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?" *Lancet Neurol.*, vol. 5, pp. 708–712, Aug., 2006.

[9] K. Migita et al. "Transcranial magnetic coil stimulation of motor cortex in patients with central pain," *Neurosurgery*, vol. 36, no. 5, pp. 1037–1039, May, 1995.

[10] N. Murase et al. "Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp," *Brain*, vol. 128, pp. 104–115, Jan., 2005.

[11] S. Rossi et al. "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research," *Clin. Neurophysiol*., vol. 120, pp. 2008–2039, Dec., 2009.

[12] U. Berger et al. "Magnetic stimulation intensity modulates motor inhibition," *Neurosci. Lett*., vol. 504, pp. 93–97, Oct., 2011.

[13] F. Maeda et al. "Inter individual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability," *Exp. Brain Res*., vol. 133, pp. 425–430, Aug., 2000.

[14] N. Lang et al. "Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability," *Clin. Neurophysiol.*, vol. 117, pp. 2292–2301, Oct., 2006.