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Intra- and interindividual variability of motor responses to repetitive transcranial magnetic stimulation

M. Sommer, T. Wu[1], F. Tergau, W. Paulus*

Department of Clinical Neurophysiology, University of Goettingen, P.O. Box 3742, D-37070 Goettingen, Germany

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Abstract

Objectives: Repetitive transcranial magnetic stimulation (rTMS) can modify cortical excitability and is widely used for clinical and research purposes. We sought to determine the intra- and interindividual variability of its effects on motor cortex excitability, and whether repeated paired-pulses yield less variability than repeated single-pulses.

Methods: We investigated rTMS over the left motor cortex of 6 healthy subjects and recorded motor evoked potentials (MEPs) from the right abductor digiti minimi muscle. Eighty single suprathreshold stimuli or conditioning-test pairs of stimuli were delivered at 2 Hz frequency. The pairs consisted of a subthreshold pulse followed by a suprathreshold pulse after 2, 5 or 10 ms. In each subject we studied all types of rTMS 5 times on separate days. Single suprathreshold pulses at 0.17 Hz preceded rTMS for baseline determination.

Results: The day-to-day variability of MEPs during either type of rTMS was small compared to the subject-to-subject variability. MEPs increased during all types of rTMS except for interstimulus interval (ISI) 2 ms. Paired-pulses yielded less variability than single-pulse rTMS.

Conclusions: Motor responses to rTMS show a high interindividual, but a low intraindividual variability. Repeated paired-pulses yield less variability than repeated single-pulses.

Keywords: Repetitive transcranial magnetic stimulation; Motor cortex excitability; Corticospinal tract

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is widely used to modulate the excitability of the human cortex (Pascual-Leone et al., 1994; George et al., 1995; Epstein, 1998; Sommer et al., 1998; Siebner et al., 1999a,b; Tergau et al., 1999). Many of these reports state a large range of interindividual responses to rTMS. A good prediction of rTMS-related effects requires detailed knowledge about the variability of individual responses to rTMS. The first aim of the present study, therefore, was to investigate systematically the inter- and intraindividual variability of motor responses to rTMS in healthy subjects.

In addition, pairs of suprathreshold stimuli are known to yield less intraindividual variability than single stimuli (Nielsen, 1996). The second aim of the present study, therefore, was to test the hypothesis that rTMS with repeated conditioning-test pairs of pulses (Sommer et al., 2001) might show less trial-to-trial variability than usual single-pulse rTMS.

2. Methods

We investigated 6 healthy subjects (average age, 28.3 years, range 28–30 years) who were recruited among the authors and the laboratory staff and were familiar to rTMS. The protocol was approved by the local ethics committee, and all participants had given written informed consent. Participants were sitting in a reclining chair with the arms and the neck supported. We applied TMS to the motor cortical representation area of the ADM of the dominant hand. Stimuli were generated by two Magstim rapid stimulators connected via a custom-built bistimulation module (The Magstim Company, Dyfed, UK). In this setup each stimulator yields a maximum magnetic field of 1.4 T. Stimuli were delivered via a figure-of-8 coil in which each wing had an outer diameter of 7 cm. Motor evoked potentials (MEPs) were recorded from the right ADM by two silver–silverchloride electrodes in a belly-tendon montage, with a sampling rate of 5000 Hz and filters at

* Corresponding author. Tel.: +49-551-3966-50; fax: +49-551-3981-26.
E-mail address: w.paulus@med.uni-goettingen.de (W. Paulus).
[1] Present address: Human Motor Control Section, Medical Neurology Branch, NINDS, NIH, Building 10, Room 5N226, 10 Center Drive, MSC 1428, Bethesda, MD 20892-1428, USA.

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10 Hz and 5 kHz (Synamps, Neuroscan Inc., Herndon, VA, USA).

The optimal motor cortical representation of the ADM muscle of the dominant hand was determined by applying suprathreshold stimuli to the head over the presumed area of the central sulcus with the handle of the coil pointing backwards and lateral. The position that yielded the highest amplitude at a given suprathreshold intensity was marked with a pen. The coil was held manually above that point. Coil position was frequently checked and corrected, if necessary. We determined motor thresholds by delivering single TMS over the optimal ADM representation and by reducing the stimulus intensity in steps of 1% stimulator output. The resting motor threshold (RMT) was defined as the lowest intensity at which at least 5 out of 10 consecutive MEPs were $\geq$50 μV in amplitude while the investigated muscle was at rest. Audiovisual electromyographic (EMG) feedback was provided to control for muscle relaxation. The lowest intensity at which 5 out of 10 consecutive MEPs were $\geq$200–300 μV in amplitude during moderate voluntary abduction of the small finger was set as active motor threshold (AMT) (Rossini et al., 1994; Rothwell et al., 1999).

rTMS consisted of either single stimuli adjusted to yield MEPs with a baseline amplitude of approximately 1.0 mV (which was equivalent to 115–125% RMT) or of repeated pairs of pulses with a conditioning pulse (intensity: 90% AMT) followed by a suprathreshold pulse of the above-mentioned intensity after 2, 5 or 10 ms (Kujirai et al., 1993; Ziemann et al., 1996; Sommer et al., 1999). As in an earlier study (Sommer et al., 2001), we applied 80 single TMS pulses or pairs of pulses at 2 Hz frequency. rTMS was preceded by 20 single suprathreshold stimuli of the above-mentioned intensity at 0.17 Hz frequency to detect the baseline level of excitability (Sommer et al., 2001). All 4 types of rTMS were tested on the same day with an inter-experiment interval of at least 1 h. Experiments were repeated on 5 consecutive days, the order of experiments on each day being randomized.

For analysis of threshold variability we calculated separate variance component analyses (ANOVA type, SPSS 10.0.7, SPSS Inc., Chicago, IL, USA) with RMT or AMT as dependent factor, 'day' and 'subject' as random factors, and 'type of rTMS' as fixed factors.

For analysis of MEP amplitude variability we measured the peak-to-peak amplitudes of MEPs before and during rTMS. All trials with incomplete relaxation in the prestimulus recording were rejected. We normalized MEP amplitudes during either type of rTMS to the corresponding baseline and grouped them in bins of 10 consecutive MEPs each. We calculated a variance component analysis (ANOVA type) with MEP amplitude as dependent factor, 'day' and 'subject' as random factors, and 'type of rTMS' and 'bin' as fixed factors.

Our second hypothesis was that rTMS with repeated conditioning-test pairs of pulses shows less trial-to-trial variability than usual single-pulse rTMS. To address this point we normalized each MEP amplitude obtained during rTMS to the mean value of all 80 MEPs recorded during the corresponding type of rTMS; we performed this normalization in all subjects for all MEPs from day 1. We then calculated the coefficient of variation. All data are indicated as mean $\pm$ standard deviation.

3. Results

The average RMT across subjects and days was 49.4 $\pm$ 7.9, the average AMT 42.2 $\pm$ 9.5. The interindividual difference contributed much more to the variability than the intraindividual variability either for RMT (Table 1). The intraindividual mean range between minimum and maximum threshold observed over 5 days was 4.3 $\pm$ 1.2% of stimulator output for RMT and 3.0 $\pm$ 1.6% for AMT.

For the MEP amplitudes, the between-subject variability contributed a much larger proportion to the total variance of the results than the day-to-day variability (Table 2). MEP amplitudes increased during the course of all types of rTMS except for interstimulus interval (ISI) 2 ms. The standard deviation was smaller during bin 1 than during bin 8 for the rTMS types of single-pulses (74.1 $\pm$ 39.4% vs. 120.8 $\pm$ 100.6%) and paired-pulses with the interval 10 ms (151.1 $\pm$ 78.2% vs. 219.5 $\pm$ 120.2%), while for the other types the standard deviation was similar in all bins. The standard deviation did not systematically increase or decrease with the number of days of testing. The example of MEPs from two representative subjects (ISI 2 ms, Fig. 1) demonstrate a large interindividual, but rather small intraindividual variability.

The coefficient of variation was smaller for paired-pulse than for single-pulse rTMS (Fig. 2).

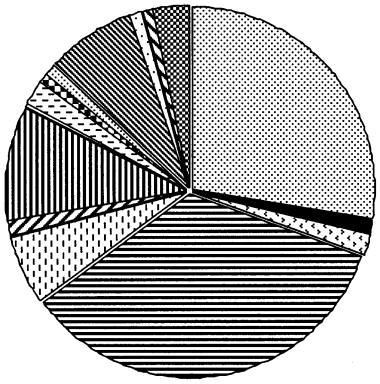
Table 1
ANOVA table of the variance component analysis for resting (a) and active (b) motor threshold

	Sum of squares	d.f.	Mean square
(a)			
Subject	6 735 742	5	1 347 148
Day	54 450	4	13 612
Type	1 425	3	475
Subject*day	297 550	20	14 877
Subject*type	17 825	15	1 188
Day*type	13 283	12	1 107
Subject*day*type	92 717	60	1 545
(b)			
Subject	10 220 467	5	2 044 093
Day	24 783	4	6 196
Type	9 967	3	3 322
Subject*day	190 617	20	9 531
Subject*type	42 333	15	2 822
Day*type	24 283	12	2 024
Subject*day*type	113 917	60	1 899

Table 2
ANOVA table of the variance component analysis for MEPS during rTMS[a]

	Sum of squares	df	Mean square
DAY	101643,401	4	25410,850
SUBJECT	2747872,072	5	549574,41
BIN	198769,149	7	28395,593
TYPE	3408535,329	3	1136178,4
DAY * SUBJECT	616102,108	20	30805,105
DAY * BIN	33516,593	28	1197,021
DAY * TYPE	217062,417	12	18088,535
SUBJECT * BIN	148772,358	35	4250,639
SUBJECT * TYPE	994908,176	15	66327,212
BIN * TYPE	82847,154	21	3945,103
DAY * SUBJECT * BIN	113159,063	140	808,279
DAY * SUBJECT * TYPE	760569,654	60	12676,161
DAY * BIN * TYPE	60896,965	84	724,964
SUBJECT * BIN * TYPE	120904,006	105	1151,467
DAY * SUBJECT * BIN * TYPE	344836,881	420	821,040

[a] A pie chart illustrating the contribution of the sum of squares to the total sum of squares is below the table. Note that the subject-related interindividual variability was considerably larger than the day-to-day intraindividual variability.



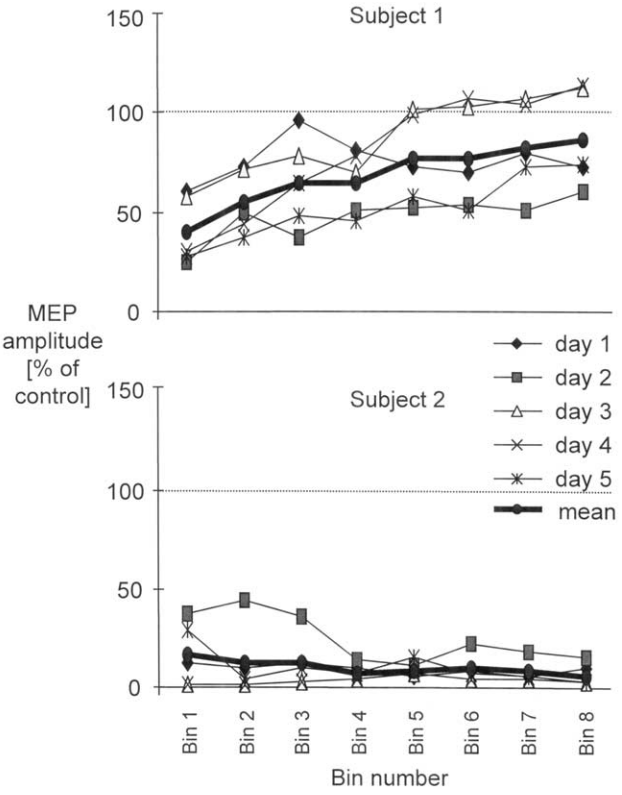


Fig. 1. MEP amplitudes from the right ADM muscle recorded on 5 days in two subjects. Data are pooled in 8 bins of 10 consecutive MEPs each. The average MEP amplitude of all 5 recordings is shown as thick line. rTMS stimuli consisted of pairs of conditioning-test stimuli with an interval of 2 ms repeated at 2 Hz frequency. Values are normalized to a baseline of single control stimuli, their amplitude is indicated as dashed line. Note that MEPs remain inhibited in subject 2 on all days, while they are steadily increasing in subject 1 on all days. This illustrates an important interindividual and a low intraindividual variability of rTMS motor responses.

4. Discussion

Our novel finding is a relatively small day-to-day variability which indicates a considerable intraindividual stability of rTMS-induced motor responses. Our results confirm a large interindividual variability of MEP amplitudes elicited by single-pulse TMS (Kujirai et al., 1993) and rTMS (Pascual-Leone et al., 1994; Tergau et al., 1997).

The intraindividual variability has been attributed to phase cancellations in MEP measurements and may be overestimated for methodological reasons (Magistris et al., 1998). The low day-to-day variability of our results is consistent with Maeda et al. (2000b), who found similar lasting effects of 1 Hz rTMS in two sessions separated by 1 week. Other authors also studied the intraindividual variability of rTMS motor responses and found a degree of variability that was similar in muscles of different limbs and only marginally affected by the magnetic coil orientation and by the temporal relationship of electrocardiogram (ECG) activity and TMS (Ellaway et al., 1998). They hypothesized that fluctuations of the excitability of the corticospinal tract, particularly on the cortical level, may be responsible for this intraindividual variability. Another group studied single-pulse TMS (Kiers et al., 1993) and found that the

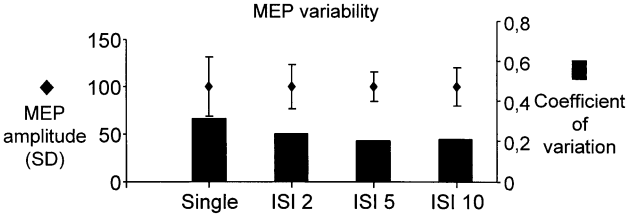


Fig. 2. Variability of MEP amplitudes from the right ADM obtained during rTMS of 4 types, data from day 1 are shown. For comparison of 4 types of rTMS (single-pulse rTMS, paired-pulse rTMS with the ISIs of 2, 5 or 10 ms) MEPs are normalized to the mean amplitude of 80 MEPs of the corresponding type of rTMS. Mean values, standard deviations and the coefficient of variation are shown. Note that the variability is lower for paired-pulse rTMS than for single-pulse rTMS.

MEP amplitude variability is larger than the H-reflex variability, supporting the idea that the major part of intraindividual variability is generated in the upper parts of the corticospinal tract.

The reason for the interindividual MEP amplitude variability is poorly understood, so is the cause of the interindividual motor threshold variability. Motor thresholds are susceptible to coil orientation, and TMS best induces currents in fibres which run horizontally to the coil (Amassian et al., 1989; Rothwell et al., 1991; Ziemann et al., 1996). Hence, a variable anatomical localization of the motor cortex representation of the hand muscles may contribute to the differences in motor threshold. Even though in our study the stimulus intensity was adjusted for motor thresholds, the interindividual range of responses may be attributed to the same anatomical variability. Our data are consistent with those of Maeda et al. (2000a) who showed that the degree of MEP amplitude enhancement observed with fast as compared to slow rTMS differs substantially among individuals.

Our results confirm an increase of MEP amplitude during rTMS of a frequency higher than 1 Hz (Pascual-Leone et al., 1994; Jennum et al., 1995; Maeda et al., 2000a,b; Sommer et al., 2001). It has been suggested that the corticospinal volley consists of several waves that increase in number and amplitude during high-frequency rTMS, and that there is a summation of excitatory post-synaptical potentials at spinal motoneurons (Amassian et al., 1989; Pascual-Leone et al., 1994). The paired-pulse rTMS results show that pairs with the ISI 2 ms are less susceptible to the frequency-induced increase than the other types of rTMS studied here. These different slopes of facilitation are related to baseline MEP size rather than ISI (Sommer et al., 2001).

Our results confirm earlier reports that paired-pulse TMS has a lower variability than single-pulse rTMS. We extend this finding from paired pulses of equal intensity (Nielsen, 1996) to conditioning-test pairs of TMS pulses. Presumably, the conditioning pulse pre-selects a range of corticospinal volleys to be triggered by the subsequent suprathreshold pulse, thus reducing the variability of resulting MEP amplitudes.

rTMS-naive subjects, healthy or impaired, may show a large degree of variability of rTMS-effects in the first (treatment) sessions. This is likely explained by a higher arousal and of sympathotonic tone (Niehaus et al., 1998; de Kloet et al., 2000). That is why in our laboratory we discard the first or the first two recordings of rTMS-naive subjects. We acknowledge that this novelty effect may limit the transfer of our findings to clinical applications. We felt, however, that the extra amount of variability related to the novelty effect would distract from the key issue of the relative proportion of intra- and interindividual variability in repeated rTMS sessions.

The interindividual differences shown in these results may help explain the differential susceptibility of individuals, healthy or impaired, to the influence of rTMS (Tergau et al., 1997, 1999; Siebner et al., 1999a). The intraindividual stability of motor responses during rTMS suggests a reliable influence of rTMS in responders, and may be useful for further attempts to modify the excitability of the motor cortex.

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