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Clinical Neurophysiology 113 (2002) 376–382

www.elsevier.com/locate/clinph

Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS)

Fumiko Maeda[a,1], Massimo Gangitano[a], Mark Thall[a], Alvaro Pascual-Leone[a,b,*]

[a]*Laboratory for Magnetic Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Kirstein Building KS 454, 330 Brookline Avenue, Boston MA, USA*

[b]*Institute for Bioengineering, Miguel Hernandez University, Alicante, Spain*

Accepted 26 December 2001

Abstract

Objectives: Previous studies have evaluated the variability of motor thresholds (MTs) and amplitude of motor-evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) within and across individuals. Here we evaluate the reproducibility and inter-hemispheric variability of measures of cortical excitability using the 'conventional' paired-pulse (PP) TMS technique.

Methods: We studied PP curves of the left and right hemisphere in 10 healthy subjects on two separate days 2 weeks apart. The inter-stimulus intervals studied were 1, 3, 6, 8, 10 and 12 ms with the conditioning stimulus being 80% of the resting MT, and a single test stimulus producing MEPs of approximately 0.8 mV peak-to-peak amplitude.

Results: As a group, the PP curves of the left and right hemispheres, and of Day1 and Day2 were not significantly different. The intracortical inhibition (ICI), but not the intracortical facilitation, showed a good correlation across days within the individuals.

Conclusions: Cortical excitability, particularly ICI, measured by PP TMS shows no inter-hemispheric asymmetry and is reproducible within individuals.

Keywords: Transcranial magnetic stimulation; Paired-pulse; Cortical excitability; Healthy subjects; Neurophysiology

1. Introduction

Transcranial magnetic stimulation (TMS) allows the non-invasive study of motor cortical excitability (Pascual-Leone et al., 1998). One of the methods available is the paired-pulse (PP) technique (Kujirai et al., 1993). In this technique two magnetic stimuli are delivered in close sequence to the same cortical region through a single stimulation coil. The first (conditioning) stimulus (CS) modifies the response to the second (test) stimulus (TS). The effects of the PP technique depend on the intensity of the CS, the interval between the stimuli (ISI) and the intensity of the TS. The intensities of the CS and TS influence the effects as different circuits are recruited by different intensities of stimulation. The ISI influences the results as the time constant of each activated circuit may differ. Here, we only discuss the 'conventional' PP paradigm, in which a subthreshold CS is followed by a suprathreshold TS at ISIs of 1–20 ms (Ziemann, 1999). Intracortical inhibition (ICI; at ISIs of 1–4 ms) and intracortical facilitation (ICF; at ISIs of 8–12 ms) appear to be due to activation of separate circuits (Ziemann, 1999). ICI seems to reflect the activity of inhibitory interneurons or inhibitory connections between cortical output cells (Wassermann et al., 1996). ICF seems to be partially due to facilitatory interactions between I waves, and is thought to take place in the motor cortex at or upstream from the cortico-spinal neuron (Ziemann et al., 1998).

Studies of cortical excitability using the PP curves can provide novel insights into the pathophysiology of various neurological and psychiatric disorders. The effects of different disorders and medications on the inhibitory and facilitatory phases of the PP curve suggest that GABAergic, dopaminergic and glutamatergic mechanisms are involved (for a review, refer to Ziemann, 1999). Enhancement of GABAergic and dopaminergic activities is predominantly associated with increase of ICI. ICF may be related to glutamatergic excitatory intracortical modulation.

The growing use of this technique forces questions about the variability of the results between individuals, hemispheres and days. It is generally thought that PP curves are fairly consistent between subjects, especially at short

* Corresponding author. Tel: +1-617-667-0203; fax: +1-617-975-5322.
E-mail address: apleone@caregroup.harvard.edu (A. Pascual-Leone).
[1] Present address: Brain Mapping Division, Neuropsychiatric Institute, UCLA School of Medicine, Los Angeles, CA, USA.

1388-2457/02/$ - see front matter CLINPH 2000186
PII: S1388-2457(02)00008-1

ISIs, with variable peak magnitude of inhibition. A normative curve has been suggested, by applying the PP technique to one hemisphere in 20 healthy subjects (Ziemann, 1999). There are very few studies, however, that examined both hemispheres within the same healthy subject (Fong et al., 1993; Maeda et al., 2000; Civardi et al., 2000), reproducibility between different sessions (Boroojerdi et al., 2000) and inter-subject and inter-investigator variability (Boroojerdi et al., 2000). It is crucial to understand the reproducibility of the PP curves on separate days together with the inter-hemispheric variability when this technique is employed in assessing the course and hemispheric laterality of dysfunction or treatment in patient populations.

In this study, we explored this issue examining the variability of cortical excitability as measured by the 'conventional' PP technique in healthy subjects: (1) on different days (reproducibility) and (2) on the left and right hemispheres (variability).

2. Methods

The study was approved by the local institutional review board (IRB) and informed written consent was obtained from all participants.

2.1. Subjects

Ten healthy volunteers (5 males and 5 females, age: mean 30.3, range 20–50 years, 9 right handed according to the Edinburgh Handedness Inventory-revised (Oldfield, 1971)) were recruited. Screening interviews confirmed that none of them had any psychiatric or medical history or contraindications for TMS (Wassermann, 1998). None were on chronic medications.

2.2. Transcranial magnetic stimulation procedure

2.2.1. Preparation

Subjects were seated in a comfortable reclining chair. They were instructed to keep their hands still and as relaxed as possible pronated on arm-rests. Tightly fitting lycra swimming caps were placed on their heads to mark the site of stimulation.

Four disposable, self-adhesive electrodes were placed on the belly and tendon of the each first dorsal interosseus (FDI) muscle prior to stimulation. Circular ground electrodes with a diameter of 30 mm were placed on the forearms and linked to common grounds.

2.2.2. Equipment

The study was performed with a 70 mm figure-of-8 coil using two magnetic stimulators (Magstim200), which were connected through a Bistim module. Motor-evoked potentials (MEPs) were collected using a Dantec Counterpoint electromyograph with an amplification of $\times 3000$ and a band pass of 20–1000 Hz. The preamplified signal was digitized and collected continuously by a CED Micro 1401 interface (sampling rate 2 kHz) and stored in a PC for off-line analysis. The CED interface also triggered random TMS pulses in the PP study.

2.2.3. Determination of optimal site

We identified the sites of stimulation over the left and right motor cortex as the scalp position from which TMS induced MEPs of maximal peak-to-peak amplitude in the contralateral FDI muscle. The coil was positioned tangentially to the scalp with the coil pointing in an antero-medial direction, 45° from the midsagittal axis of the subject's head. This coil placement was chosen based on the finding that the lowest motor threshold (MT) is achieved when the induced electric current in the brain is flowing approximately perpendicular to the orientation of the central sulcus (Brasil-Neto et al., 1992).

2.2.4. Determination of motor threshold

MT was defined as the minimal intensity of stimulation capable of inducing MEPs greater than 50 μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials. Single pulse TMS was delivered to the optimal scalp positions and the MEPs evoked in the contralateral FDI were recorded. Stimulation began at well above threshold intensity (generally 90% of the stimulator output) and decreased in steps of 2% of the stimulator output. This procedure was carried out at the beginning of all PP studies and separately for each hemisphere.

2.2.5. Paired-pulse technique

The PP TMS study followed the method of Kujirai et al. (1993). The CS was applied at 80% of the subject's MT and was confirmed to induce no MEPs. The TS was applied at approximately 130% of the subject's MT and was adjusted to evoke MEPs of approximately 0.8 mV peak-to-peak amplitude (± 0.2 mV). The ISIs were 1, 3, 6, 8, 10 and 12 ms. There were 10 trials per condition (6 different ISIs and conditions with CS alone or TS alone) which was balanced and divided into two blocks. The order of the trials (either CS or TS alone, or PP with an ISI of 1, 3, 6, 8, 10 or 12 ms) was random. There was an 8 s interval between each trial.

All data acquisition was conducted during complete muscle relaxation that was monitored by on-line audio and visual electromyogram (EMG) signals 50 ms prior to the application of the TMS and for a duration of 4000 ms. The whole TMS procedure was carried out on Day1, and 2 weeks later approximately at the same time of the day (Day2). The order of the hemisphere to be studied first was randomized and counterbalanced across subjects. The same coil was used throughout the study.

2.3. Data analysis

Rectified area-under-the-curve of the 10 MEPs recorded

at each ISI for each subject was averaged. These values were compared to the MEP areas of TS. For each ISI a percent difference in MEP area to the TS alone was computed, such that negative values reflect inhibition and positive values reflect facilitation.

First, we analyzed the MT since it is relevant in interpreting the PP results. This was done by a 2(Day1 and Day2) × 2(left and right Hemispheres) repeated measures analysis of variance (ANOVA).

For the results obtained from the PP technique, the 6 ISIs were grouped into 3 groups depending on the known mechanism of action to increase power. The shorter ISIs (1 and 3 ms) was grouped as ICI, the intermediate ISIs (6 and 8 ms ISI) were grouped into Intermediate and the longer ISIs (10 and 12 ms) were grouped into ICF. All ISIs were examined employing (1) a 2(Day1 and Day2) × 2(left and right Hemispheres) × 3(ICI, Intermediate and ICF) repeated measures ANOVA. Since there was a 3-way interaction (see Section 3), the nature of this interaction was explored by (2) a 2(Day1 and Day2) × 2(left and right Hemispheres) repeated measures ANOVA for each grouped ISIs (ICI, Intermediate and ICF). Hereafter, all the analysis was done separately for the examination of the reproducibility within the two separate study days and the variability within the left and right hemispheres. First we conducted planned comparisons separately (3) within Day1 and Day2 to examine the reproducibility across time and (4) within the left and right Hemispheres to examine the variability across hemispheres. Further, to explore the reproducibility across time, (5) linear regression models were applied to correlate each ISI between Day1 and Day2. To explore the variability across hemispheres, (6) linear regression models were applied to correlate each ISI between the left and right Hemispheres. Finally, (7) the Spearman–Brown formula was applied to obtain reliability coefficients. The significance level was set at $P = 0.01$ uncorrected for multiple comparisons.

3. Results

With regard to safety, all subjects tolerated the study well without unexpected complications. The only side effect of the stimulation was a mild transient headache in one subject. The headache resolved promptly with mild analgesia (acetaminophen).

3.1. Motor threshold

The mean MT on Day1 was 46.9% (standard error, SE = 2.59) of maximum output of the magnetic stimulator for the left and 44.3% (SE = 2.56) for the right hemisphere. On Day2, the mean MT was 47.7% (SE = 2.43) for the left and 44.9% (SE = 2.39) for the right hemisphere. There was no interaction for factors Hemispheres (Left and Right) × Days (Day1 and Day2) ($F(1,9) = 0.09$, $P = 0.77$). Main effect for Hemisphere ($F(1,9) = 1.64$, $P = 0.23$) or for Days ($F(1,9) = 2.92$, $P = 0.12$) was also found to be non-significant.

3.2. Paired-pulse curve

3.2.1. General

The PP curve for each ISI is displayed in Fig. 1. The mean stimulus intensity for the CS on Day1 was 37.5% (SE = 1.97) for the left and 35.4% (SE = 1.84) for the right hemisphere, and on Day2, 38.2% (SE = 1.84) for the left and 35.9% (SE = 1.81) for the right hemisphere. The mean stimulus intensity for the TS on Day1 was 48.8% (SE = 2.56) for the left and 46.1% (SE = 2.53) for the right hemisphere, and on Day2, 49.6% (SE = 2.40) for the left and 46.7% (SE = 2.35) for the right hemisphere. No MEPs were elicited from the trials when only a subthreshold CS was applied. The mean MEP amplitudes for the TS on Day1 was 0.86 mV (SE = 0.20) for the left and 0.90 mV (SE = 0.22) for the right hemisphere, and 0.77 mV (SE = 0.16) for the left and 0.92 mV (SE = 0.21) for the right hemisphere on Day2.

A 2(Day1 and Day2) × 2(left and right Hemispheres) × 3(ICI, Intermediate and ICF) repeated measures ANOVA was performed. There was an overall 3-way interaction across the variables for factors Hemispheres (Left and Right) × Days (Day1 and Day2) × ISIs (ICI, Intermediate and ICF) ($F(2,38) = 6.60$, $P = 0.004$) (Fig. 2). There was a significant main effect found for ISI ($F(2,38) = 145.55$, $P = 0.0001$). There was no main effect for Hemisphere ($F(1,19) = 0.74$, $P = 0.40$) or Day ($F(1,19) = 0.16$, $P = 0.70$). In addition, none of the two-way interactions were significant (Day × Hemisphere: $F(1,19) = 2.96$, $P = 0.10$; Day × ISI: $F(2,38) = 1.59$, $P = 0.22$; Hemisphere × ISI: $F(2,38) = 1.31$, $P = 0.28$) (Fig. 2). All ISIs were significantly different from each other (ICI vs. Intermediate, ICI vs. ICF and Intermediate vs. ICF; all Ps = 0.0001).

The 3-way interaction, shown in Fig. 2, appeared to be due to a two-way interaction between Day and Hemisphere, present only for the longer ISIs (ICF). This interpretation was confirmed by performing separate ANOVAs for the ICI, Intermediate and ICF. For ICI, the 2(Day1 and Day2) × 2(left and right Hemispheres) repeated measures ANOVA showed no significant interaction for factors Hemispheres (Left and Right) × Days (Day1 and Day2) ($F(1,19) = 1.56$, $P = 0.23$) nor main effect for Day ($F(1,19) = 3.75$, $P = 0.07$) nor for Hemisphere ($F(1,19) = 1.42$, $P = 0.25$). For Intermediate, too, the 2(Day1 and Day2) × 2(left and right Hemispheres) repeated measures ANOVA showed no significant interaction for factors Hemispheres (Left and Right) × Days (Day1 and Day2) ($F(1,19) = 0.37$, $P = 0.55$) nor main effect for Day ($F(1,19) = 1.33$, $P = 0.26$) nor for Hemisphere ($F(1,19) = 0.44$, $P = 0.52$). For ICF, however, the 2(Day1 and Day2) × 2(left and right Hemispheres) repeated measures ANOVA showed a marginally significant interaction for factors Hemispheres (Left and Right) × Days (Day1

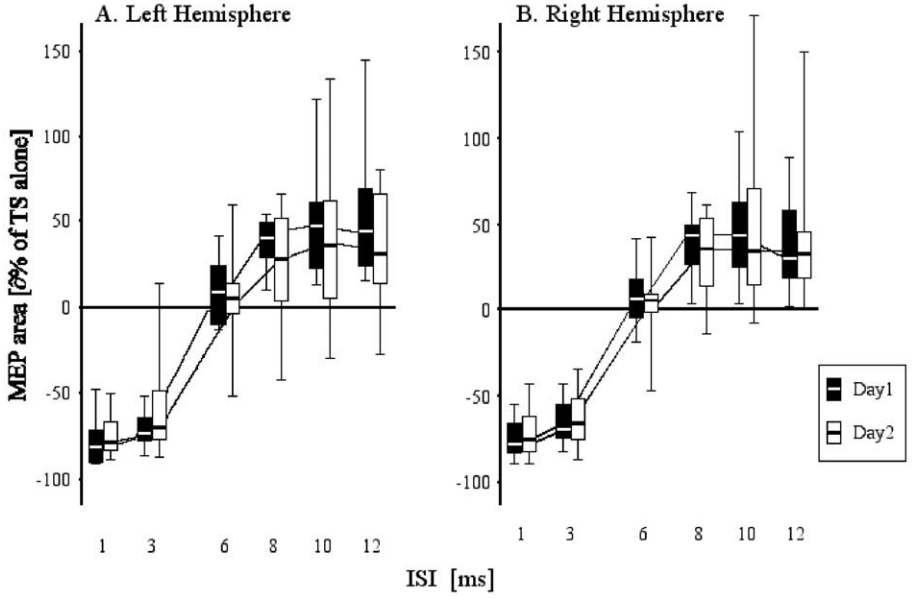

Fig. 1. PP curves for each ISI of the left (A) and right (B) hemispheres (Day1 in white lines and black boxes, and Day2 in black lines and white boxes). The box limits indicate 25th and 75th percentiles. The horizontal lines indicate the median. The whiskers indicate the range of the averaged data. Abbreviations: ∂%, percent change; MEP, motor-evoked potential; TS, test stimulus.

and Day2) ($F(1, 19) = 6.90$, $P = 0.017$), but no significant main effect for Day ($F(1, 19) = 0.22$, $P = 0.64$) nor for Hemisphere ($F(1, 19) = 1.23$, $P = 0.28$).

3.2.2. Reproducibility across time

Further, planned comparisons were explored using paired *t* tests. At each ISI, the data from Day1 was compared with that of the same hemisphere of Day2 (e.g. ICI of the left hemisphere on Day1 was compared with ICI of the left hemisphere of Day2). All comparisons were non-significant. The complete set of *P*-values is listed in Table 1. This indicates that there was no significant change across testing.

To determine the within subject consistency across the study days, a series of correlations were performed for the left and right hemispheres at each ISI. There was a significant correlation across the two study days for 1 and 3 ms ISIs for the left hemisphere and for the right hemisphere. All *r*- and *P*-values, and reliability coefficient values are listed in Table 1. We further applied the Spearman–Brown

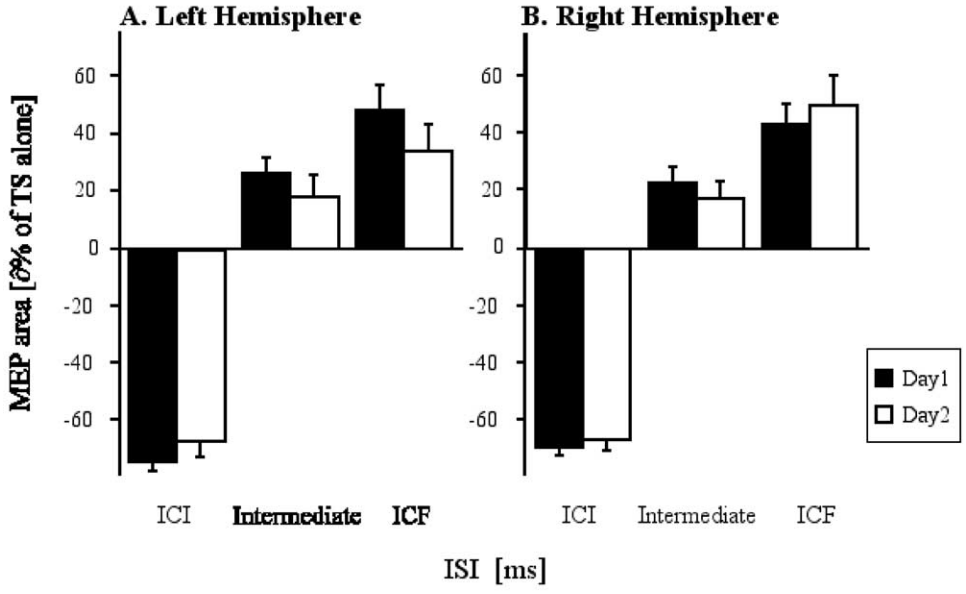

Fig. 2. PP bar charts for the shorter (ICI; 1 and 3 ms), Intermediate (6 and 8 ms) and longer (ICF; 10 and 12 ms) ISI groups of the left (A) and right (B) hemispheres (Day1 in black boxes, and Day2 in white boxes). The bars indicate standard error.

Table 1
Details of the analysis to test for reproducibility across time[a]

ISI (ms)	Lt Hemi	Rt Hemi	Day	ISI (ms)	*r*	*P*	RC
ICI	0.13	0.32	Day1	1	0.86	0.001	0.92
Intermediate	0.25	0.27		3	0.88	0.0008	0.94
ICF	0.22	0.38		6	0.77	0.009	0.87
				8	0.77	0.008	0.87
				10	0.88	0.0007	0.94
				12	0.74	0.01	0.85
			Day2	1	0.73	0.01	0.84
				3	0.85	0.001	0.92
				6	0.97	0.0001	0.98
				8	0.82	0.003	0.90
				10	0.80	0.005	0.89
				12	0.80	0.005	0.89

[a] *P*-values for planned comparisons between Day1 and Day2 for each ISI group (ICI, Intermediate and ICF) and each hemisphere. *r*- and *P*-values for correlations between Day1 and Day2 for each ISI and each hemisphere. Reliability coefficients (RCs) are also expressed.

formula ($2r/(1 + r)$) to obtain the reliability coefficient for the two study days (Table 1). This indicates that, within each individual, shorter ISIs (ICI) correlated with the other testing day and were more reproducible among all tested ISIs for the left and for the right hemispheres.

3.2.3. Variability across hemispheres

Again, planned comparisons were carried out using paired *t* tests. At each ISI, the data was compared with that of the other hemisphere of the same day (e.g. ICI on Day1 of the left compared to the right hemisphere). None of these comparisons were significant. The complete set of *P*-values is listed in Table 2. This indicates that there was no significant inter-hemispheric asymmetry mainly for the shorter and intermediate ISIs.

To determine the within subject consistency across the study days, a series of correlations were performed for the left and right hemispheres at each ISI. There was a significant correlation across the two study days for all ISIs for the left and right hemispheres. All *r*- and *P*-values, and reliability coefficients are listed in Table 2. Again, we further applied the Spearman–Brown formula ($2r/(1 + r)$) to obtain the reliability coefficient for the two study days. This indicates that, within each subject, the left and right hemispheres correlated and were *not* significantly asymmetrical for all tested ISIs for Day1 and for Day2 (Table 2).

All the above held true even when females and males were analyzed separately or when the one left-handed person was excluded.

4. Discussion

In this study, we have investigated cortical excitability of the left and right motor cortex measured by the 'conventional' PP TMS technique in healthy subjects on two separate days. The PP curves revealed no significant variation within subjects and within hemispheres on each of the two study days. Results at shorter ISIs (ICI) were found to be more reproducible than those at longer ISIs (ICF). This suggests the reproducibility of the PP curves across 2 testing days. In addition, the PP curves revealed no significant variation within subjects and within the same testing days on the left and right hemispheres. Results at all tested ISIs were found to be significantly correlated between hemispheres within the same testing day. This suggests that the inter-hemispheric variability of the PP curves is minimal across hemispheres.

We will further discuss both the reproducibility and the inter-hemispheric variability separately.

4.1. Reproducibility

Although, there is only one study that investigated the reproducibility of the PP curves (Boroojerdi et al., 2000), MT have been studied extensively in healthy subjects to investigate their reproducibility. It has been reported that

Table 2
Details of the analysis to test for variability across hemispheres[a]

ISI (ms)	Day1	Day2	Hemisphere	ISI (ms)	*r*	*P*	RC
ICI	0.36	0.96	Lt Hemi	1	0.78	0.008	0.88
Intermediate	0.74	0.94		3	0.76	0.01	0.86
ICF	0.76	0.47		6	0.33	0.34	0.50
				8	0.55	0.09	0.71
				10	0.40	0.25	0.57
				12	0.43	0.20	0.60
			Rt Hemi	1	0.70	0.02	0.82
				3	0.91	0.0002	0.95
				6	0.97	0.0001	0.98
				8	0.41	0.23	0.58
				10	0.44	0.20	0.61
				12	0.62	0.05	0.77

[a] *P*-values for planned comparisons between left hemisphere (Lt Hemi) and right hemisphere (Rt Hemi) for each ISI and each study day. *r*- and *P*-values for correlations between Lt Hemi and Rt Hemi for each ISI and each hemisphere. Reliability coefficients (RCs) are also expressed.

absolute threshold values may be useful for longitudinal studies (Ziemann et al., 1998), and there is one study which has carefully evaluated the repeatability of this measure over time (Mills and Nithi, 1997). Although we did not explore extensively since evaluation of the MT was not the main goal of our study, we did not find any significant inter-session differences.

In the one study that examined the reproducibility of ICI and ICF using the PP paradigm (Boroojerdi et al., 2000), 4 healthy subjects were studied by 3 investigators and over 3 sessions. They examined the impact of 'subject', 'session' and 'investigator' on the reproducibility of ICI and ICF. They found a high rate of inter-subject variability compared to inter-session and inter-investigator variability. Inter-session variability decreased as the number of trials collected was increased from 5 to 20. In our study, we examined the inter-session variability over two sessions and with 10 subjects with 10 trials per ISI. As in our study, their study examined the effect by grouping all the studied ISIs (1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15 and 20 ms) into 3 groups: ICI, intermediate and ICF. Their study too, found no significant effect for the factor 'session'. Although the range of the averaged data was fairly large in our study, the correlation between the two study days was significant for shorter intervals. This indicates that not ICF but ICI may be reproducible.

An interesting finding is the change in cortical excitability related to the menstrual cycle phase in healthy women (Smith et al., 1999). Although we did not find significant changes across the 2 week period studies in the females included in our study, this is certainly an important factor to consider in future experiments measuring cortical excitability.

4.2. Inter-hemispheric variability

Although no studies investigated the inter-hemispheric variability of the PP curves which have been conducted until recently (Civardi et al., 2000), MT have been studied extensively in healthy subjects to investigate their variability. Inter-hemispheric MT differences were found not to be significant, when a 'biphasic' TMS and a lateralized coil positioning are employed (Rossini and Rossi, 1998). This parameter is remarkably less variable than absolute threshold values (Cicinelli et al., 1997), and therefore is thought to reliably test patients with uni-hemispheric lesions of various etiologies (Traversa et al., 1997). Whether MT can physiologically vary because of hemispheric dominance is not clear and studies have yielded controversial results (McDonnell et al., 1991; Priori et al., 1999; Triggs et al., 1999). Age seems to play a role when inter-hemispheric differences in MT and silent period threshold are examined, in that, younger subjects appear more likely to reveal asymmetries (Matsunaga et al., 1998). Once again, in our study, we did not find any significant inter-hemispheric differences.

Fewer studies have examined the inter-hemispheric variability of the PP curve. PP curves between hemispheres in healthy subjects, investigated as controls for a group of patients with major depression, were found not significantly different (Maeda et al., 2000). Civardi et al. (2000) however, found lateralization in cortical excitability as measured by PP curves in right-handed healthy subjects, but not in left-handers. Their study, however, does not necessarily contradict our present findings. First, our sample size does not allow examination of the effect on handedness (only one left-hander). They studied 9 right-handers (5 males and 4 females) and 6 left-handers (one male and 5 females). Furthermore, the ISIs at which Civardi et al. found significant hemispheric asymmetry were not included in our study (4, 14 and 16 ms). In addition, there are other methodological differences, such as the type of coil (in their study, a non-focal large round coil was used), difference in stimulus intensities (in their study, CS: 80% of active MT, TS: 120% of resting MT) and study design (in their study, same ISIs were presumably blocked and the 4 TS and CS were randomly assorted). Any of these factors may have accounted for the difference in the findings of these two studies.

Although our results would benefit from further replication with a larger sample, homogeneous gender and handedness, different age groups and a longer interval between replications repeated multiple times, our findings provide further information on reproducibility, and the first documentation of the hemispheric correlation of PP curves over two study days in healthy subjects. These results have particular relevance for studies of patients with neurological and psychiatric disorders aimed at assessing differences between hemispheres or studying the course of a disease or treatment outcome.

Acknowledgements

The authors thank Janice M. Rayman, PhD and Julian Keenan, PhD for assistance with the statistical analysis of the data. Supported in part by grants from the Cellular Science Research Foundation, Yoshida Science Foundation and the Japan North America Medical Exchange Foundation to F.M., MD; and an Independent Investigator Award from the National Alliance for Research and Schizophrenia and Depression and grants from the Stanley Vada Foundation and the National Institutes of Mental Health (RO1MH57980) to A.P.-L., MD, PhD.

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