

Inter-pulse Interval Affects the Size of Single-pulse TMS-induced Motor Evoked Potentials: A Reliability Study

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ABSTRACT

Introduction: Measuring the size of motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) is an investigational technique to show the level of corticospinal excitability; however, some of the fundamental methodological aspects of TMS (such as the effects of inter-pulse intervals (IPI) on MEP size) are not fully understood, this issue raises concerns about the reliability of MEPs, especially in pre-test post-test studies.

Methods: MEP size at short and long IPIs was assessed during two separate sessions. Inter- and intra-session reliability of MEP size also was assessed at both short and long IPIs.

Results: The results indicated that long IPIs induced larger MEPs ($P < 0.05$) across all time points. The intra-class correlation coefficient (ICC) indicated high intra- and inter-session reliability for short (0.87 to 0.96) and long (0.80 to 0.97) IPIs respectively. The amplitude of MEPs also had high intersession reliability for short (ICC=0.87) and long (ICC=0.80) IPIs.

Discussion: This study provides evidence that the length of IPIs determines the size of MEPs. As a result, it is recommended to add the length of IPI to the international checklist of considerations for TMS application.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive, safe and painless technique for assessment of corticospinal excitability (CSE) in both healthy individuals and patients with neurological conditions. One of the major advantages of TMS is the ability of the magnetic pulses to pass unchanged through the scalp in order to induce an electric field within the conductive brain tissues (Wassermann, 2002). When applied over the primary motor cortex (M1) of a target muscle, it induces a response known as the motor evoked potential (MEP). MEPs can be recorded using surface electromyography (EMG) electrodes placed over the muscle of interest (Wassermann, 2002; Malcolm et al., 2006). Two characteristics of recorded MEPs are amplitude and latency; the amplitude provides valuable information about the excitability of corticospinal pathways.

TMS-induced MEPs have been used as a reliable outcome measure of CSE changes in a range of research protocols (Nitsche and Paulus, 2000a). Larger MEP amplitudes indicate higher CSE and smaller amplitudes indicate lower CSE (Nitsche and Paulus, 2000a; Di Lazzaro et al., 2004).

While the latency of MEP is relatively stable, the size of these responses is highly changeable (Kiers et al., 1993). Many factors can affect MEP size. Technical factors include coil type (Fleming et al., 2012), placement (Ngomo et al., 2012), orientation (Thomson et al., 2013) and TMS intensity (Fisher et al., 2002). Physiological factors include muscle fatigue (Milanovic et al., 2013), background muscle activity (Ngomo et al., 2012), arousal, attention, emotional context, and afferent feedback of different parts of the brain (such as the supplementary motor area or dorsal premotor cortex) (Schmidt et al., 2009).

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Although TMS has been employed as an investigational technique for more than two decades, some of its fundamental methodological principles are not fully understood. For instance, TMS inter-pulse interval (IPI) may have profound effects on MEP size. Even though, work in our laboratory conducted over the past 5 years suggests induction of larger MEPs with longer IPIs. To the best of our knowledge, this relationship has not been reported in the literature up to date which may be associated with a net drop in haemoglobin levels following each stimulation, this may reduce the neural activation in stimulated area for about 8-10 seconds and may affect the size of MEPs (Thomson et al., 2012b).

An important aspect of any clinical or experimental assessment tool and method is its test-retest reliability (Schmidt et al., 2009). Reliability refers to the consistency of measurements; it tests the stability of scores over time and the degree to which repeated measurements provide similar results (de Vet et al., 2006). To be an effective assessment tool, the size of TMS-induced MEPs must be reliable. A reliable measurement of MEPs guarantees stable amplitude size over time in the absence of an intervention (Lexell and Downham, 2005; Christie et al., 2007). If the IPIs of TMS pulses affect the size of MEPs, then we should avoid using different IPIs in pre-test post-test study designs. For example, if we use lower TMS IPIs (e.g. four seconds) during baseline measurements we must use identical IPIs for post intervention measurements. If we fail to do so, IPI length becomes a confounding variable and contaminates the intervention effects.

The primary aim of this study was to investigate the effects of shorter (four-second) and longer (10-second) IPIs on the size and reliability of the induced MEPs. We hypothesised that longer IPIs induce larger MEPs. We also hypothesised that longer IPIs induce more reliable MEPs.

2. Methods

Twelve healthy volunteers (six women and six men) with a mean age of 32.27 (SD=7.2 years) a mean weight of 70.9 (SD=11.4 kg) and mean height of 173.8 (SD=7.3 cm) were tested in two sessions separated by at least 48 hours. All participants were consistent right-handers according to the 10-item version of the Edinburgh Handedness Inventory (mean laterality index=100) (Oldfield 1971) with no neurological, psychological, or endocrinological problems. None were taking any medication. Prior to the experiments, all participants completed the

Adult Safety Screening Questionnaire (Keel et al., 2001) to determine their safety for TMS application. Participants gave informed consent according to the declaration of Helsinki. Monash University's Human Research Ethics Committee approved the experimental procedure. Each subject was tested at the same time of the day to avoid diurnal variation.

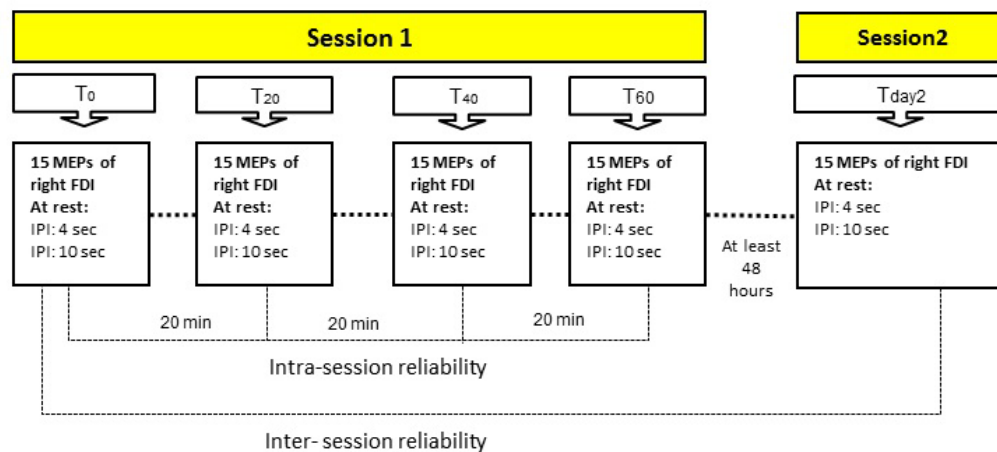
2.1. EMG recording

Participants were seated upright in an adjustable podiatry chair with head and neck supported by a headrest and the right forearm on the armrest with the wrist joint in a pronated and neutral position. To ensure good surface contact and reduce skin resistance, a standard skin preparation procedure of cleaning and abrading was performed for each site of electrode placement (Gilmore and Meyers, 1983). MEPs were recorded from the first dorsal interosseous (FDI) muscle at rest, using pregelled self-adhesive bipolar Ag/AgCl disposable surface electrodes with an inter-electrode distance of 2 cm (measured from the centres of the electrodes). The location of the FDI muscle was determined based on anatomical landmarks and observations of muscle contraction in the testing position (index finger abduction) (Kendall et al., 1983).

The accuracy of EMG electrode placement was verified by asking the subject to maximally contract the muscle while the investigator monitored online EMG activity. The ground electrode was placed ipsilaterally on the styloid process of the ulnar bone (Oh 2003) and secured with tape. All raw EMG signals were band-pass filtered (10-500 Hz), amplified ($\times 1000$) and sampled at 1000 Hz and collected on a PC running commercially-available software (LabChart™ software, AD Instruments, Australia) via a laboratory analogue-digital interface (The PowerLab 8/30, ADInstruments, Australia) for later offline analysis.

2.2. Procedure

All individuals participated in two experimental sessions. The protocol in session 1 enabled us to study the within-session reliability of MEPs (intra-session reliability). The CSE of the FDI's representation in M1 was assessed before and after 20 minutes of no intervention. Follow-up assessments were carried out at four consecutive time points (T_0 , T_{20} , T_{40} , T_{60}), 20 minutes apart. The EMG electrodes were left in place and the TMS coil was removed while the subjects rested between the pre and post measurements, with no hand or wrist movements allowed.



IPI: Inter pulse interval
FDI : First dorsal interosseous

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Figure 1. Experimental set-up; TMS was delivered on first dorsal interosseus (FDI) hotspot and 15 MEPs were recorded during a two-session experiments with at least 48 hours separation. Randomization of the short and long IPIs' order were applied at both sessions.

Each participant's second session of testing was occurred at least 48 hours after the first one. This session was shorter and involved recording of MEPs at a single time point (T_{day2}). Comparison of these data with the T_0 from session 1 enabled us to study the inter-session reliability of the MEP sizes (Figure 1). Randomization of the short and long IPIs' order were applied at both sessions.

2.3. CSE measurement by TMS

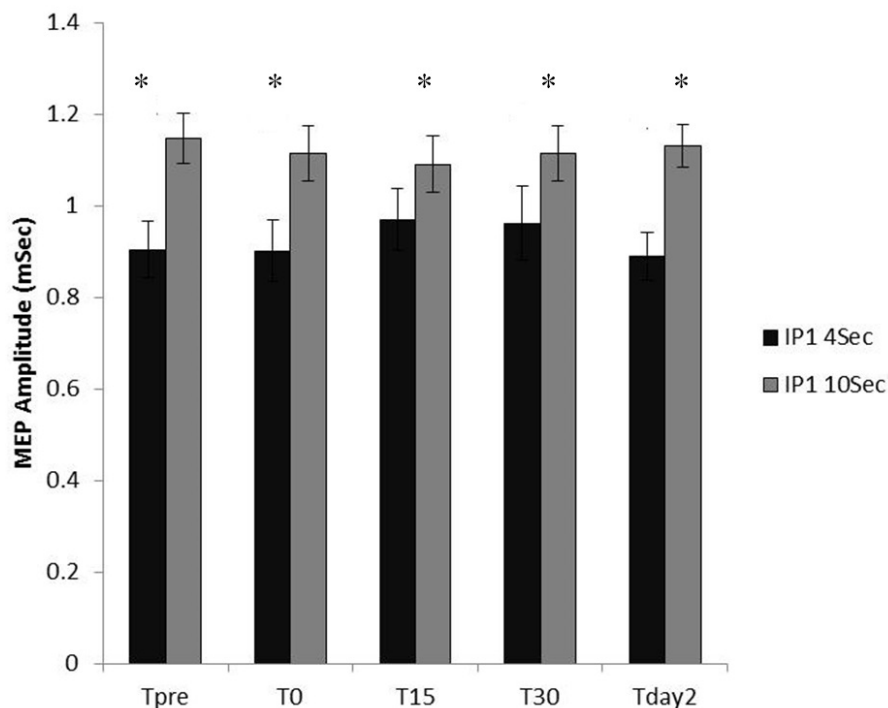
Single-pulse magnetic stimuli were delivered using a Magstim 200² (Magstim, UK) stimulator with a flat 70 mm figure-of-eight magnetic coil. Using the international 10-20 system, the vertex (Cz) point was measured and marked for the use as a reference. The magnetic coil was placed over the left M1 area, contralateral to the target muscle. The coil was set at 45° to the midline and tangential to the scalp, such that the induced current flowed in a posterior-anterior direction (Rossini and Rossi, 1998; Schmidt et al., 2009). To determine the optimal site of stimulation (hotspot), the coil was moved around the M1 of the target muscle to find the area with the largest MEP responses.

After localizing the optimal stimulation site, the coil position was marked on the scalp to ensure consistency in placement throughout the testing session. The full hotspot identification procedure was performed in each session. Resting motor threshold (RMT) was defined as the minimal stimulus intensity that evoked five MEPs

in the series of 10 tests with an amplitude of at least 50 μ V from the FDI hot spot (Devanne et al., 2006). The RMT for each subject was determined by increasing and decreasing stimulus intensity in 1-2% intervals until MEPs of appropriate size were elicited (Rothwell et al., 1999). Fifteen stimuli were delivered (Bastani and Jaberzadeh, 2012) to assess CSE at each time point, with the stimulus intensity set at 120% of each individual's RMT. The stimulus intensity remained constant throughout the study session for each subject. The excitability of M1 related to the FDI muscle was tested with both short and long IPIs randomly in two separated blocks of 15 MEPs (Bastani and Jaberzadeh, 2012). Short IPI was defined as a four-second rest between each pulse and long IPI was defined as a ten-second rest.

2.4. Data management and data analysis

The average of 15 MEPs at each time point (T_0 , T_{20} , T_{40} , T_{60} , and T_{day2}) was calculated for both short and long IPIs. Data analysis was carried out in two phases. In phase A, a two-way repeated measure ANOVA was used to study the effects of IPI on the size of TMS evoked MEPs. The first within-subject independent factor was IPI (two levels). The second independent factor was time points (five levels). Mauchly's sphericity test was used to validate an assumption of repeated measures factor ANOVA. Greenhouse-Geisser corrected significance values were used when sphericity was lacking. Post hoc comparisons were performed when sphericity was lacking. Post hoc comparisons were performed using the



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Figure 2. Comparison of short and Long IPIs in each time point of measurement. * indicates statistically significant ($P < 0.05$) and each column represents mean percentage change \pm SEM.

least significance difference (Bonferoni) adjustment for multiple comparisons when appropriate. In phase B, the within- and between-session reliability of elicited MEP sizes for both IPIs were calculated using Intra Class Correlation (ICC) (Pourtney and Watkins, 2000). To assess the agreement between the repeated measurements, a one-way ANOVA was carried out for each interval. The reliability coefficient ranges from 0 to 1, with values closer to 1 representing stronger reliability. Although the interpretation of ICCs is subjective, it has been suggested that coefficients below 0.50 represent poor reliability, those from 0.50 to 0.75 correspond to moderate reliability, and values above 0.75 indicate high reliability (Pourtney and Watkins, 2000).

3. Results

3.1. Comparison of short and long IPIs

Long IPIs (10 seconds) yielded significantly greater mean MEP amplitude than short IPIs (four seconds) (Figure 2). Table 1 depicts the MEP amplitudes; the differences between short and long IPIs were significant at all time-points.

3.2. Reliability of TMS-induced MEPs

3.2.1. Intra-session reliability

The RMT and consequent stimulus intensity (120% RMT) for the FDI muscle were 43.2% (SD=9.87) and 51.78% (SD=12.38) of stimulator output respectively. MEP amplitude changed minimally: repetition of the measurements by the same examiner every 20 minutes after the first test revealed no significant differences in group mean values. Repeated measures ANOVA revealed no significant time effect on any of the MEP measurements. ICCs ranged from 0.80 to 0.91 for IPIs of four seconds and 0.79 to 0.96 for IPIs of 10 seconds. MEP amplitudes showed high within-session reliability for both four and 10-second IPIs (Table 1).

3.3. Inter-session reliability

The averaged RMTs and consequent stimulus intensities for short and long IPIs were 37% (SD=8.94) and 44.4% (SD=12.6) of stimulus output respectively. Comparing the mean MEP amplitude after applying long and short IPIs represented more consistency in MEP amplitudes after applying TMS with long IPI. Moreover, repetition of the measurements by the same examiner in

Table 1. Comparison of short and long IPIs at five measurement points by two-tailed, paired t-test.

	T ₀ (IPI: 4-10 Sec)	T ₂₀ (IPI: 4-10 Sec)	T ₄₀ (IPI: 4-10 Sec)	T ₆₀ (IPI: 4-10 Sec)	T _{day2} (IPI: 4-10 Sec)
P-value	0.000	0.000	0.03	0.000	0.003
T (11)	-5.58	-6.52	-2.48	-4.92	-3.78

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two different sessions held an average of 48 hours apart did not reveal any significant differences in mean MEP amplitude values. A paired T-test comparing the means of the size of MEPs between the two sessions showed no significant differences for the FDI muscle. According to the ICC, all MEP amplitude measures were highly reliable for both short and long IPIs. Despite the ICC values, the standard errors of measurement (SEM) values were relatively low, suggesting the measurements were precise (Table 2).

4. Discussion

4.1. Comparison of short and long IPIs

We hypothesized that an IPI of 10 seconds would induce larger MEPs than an IPI of four seconds. This hypothesis is strongly supported by the results of the present study. While no direct similar studies exist, some studies in literature support our finding. In a near infrared spectroscopy (NIRS) study, the level of oxyhaemoglobin (HbO) decreased following each single-pulse TMS due to the contraction of vessels in the stimulated area, and a period of 8-10 sec was needed in order to return to original state (Thomson et al., 2012b). In a similar study, Thomson et al., (2011) showed that each TMS pulse stimulates smooth muscles in the walls of blood vessels and reduces blood flow for 8–10 seconds (Thomson et al., 2011). As a result, it can be concluded that TMS pulses can change the hemodynamic statute of stimulated areas (Thomson et al., 2012a).

The finding of the current study is supported by those of rTMS studies in which the reduction of HbO led to elicitation of smaller MEPs (Fitzgerald et al., 2006; Thomson et al., 2012b). Significant reduction in HbO, which was observed with 130% rTMS, suggested that normal hemodynamic homeostatic mechanisms might be disrupted by TMS pulses. HbO concentration began to increase about four seconds after onset of TMS pulses and finally returned to normal levels after 15 seconds (Mochizuki et al., 2006). It seems that vasoconstriction resulting from suprathreshold TMS disrupts constant perfusion in stimulated area (Mochizuki et al., 2006; Vernieri et al., 2009). These findings show that neurons in the stimulated area need at least 10 seconds to return to optimal state with maximum delivery of oxygen for peak performance. This mechanism easily explains smaller MEP sizes with a shorter IPI: when using an IPI of four seconds, the stimulus applies while the blood circulation in the stimulated area is not in an optimal state. Therefore, due to vasoconstriction after each TMS stimulus (Rollnik et al., 2002; Speer et al., 2003), the ability of the hemodynamic system is diminished and neurons cannot mount a proper response.

Given that a direct relationship exists between regional cerebral blood flow (rCBF) and excitatory synaptic activity (Mochizuki et al., 2004), the other probable mechanism is that vasoconstriction following TMS stimuli decreases the level of excitatory activity in the stimulated area. This may lead to decreased MEP sizes. It is likely that larger IPIs provide enough time for rCBF and excitatory circuits to return to the normal levels associated with larger MEPs.

Table 2. Comparison of intra- and inter-session reliability of short and long IPIs by Inter Class Correlation (ICC) and Standard Error of Measurement (SEM).

IPI	Intra-session reliability						Inter-session reliability		
	ICCs						SEM (%)	ICCs	SEM (%)
	T ₀ -T ₂₀	T ₀ -T ₄₀	T ₀ -T ₆₀	T ₂₀ -T ₄₀	T ₂₀ -T ₆₀	T ₀ -T ₂₀ -T ₄₀ -T ₆₀		T ₀ -T _{day2}	
4 Sec	0.91	0.95	0.96	0.96	0.94	0.96	1.2	0.87	1.3
10 Sec	0.86	0.83	0.86	0.93	0.97	0.95	1.7	0.80	2.2

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4.2. Reliability of TMS-induced MEPs at larger IPIs

The shape, size, orientation of the TMS coil, and direction of the induced current flow may affect the size of MEPs. All these factors were similar in all measurement points (Hallett and Chokroverty, 2005). Moreover, the other factor that could theoretically affect MEP amplitudes' reliability is the use of a neuro navigation system in eliciting MEPs. However, two recent studies found no decrease in the variability (Jung et al., 2010) and no further improve in reliability (Fleming et al., 2012) of MEPs with TMS navigated systems. In the current study, we used a conventional TMS assessment technique without a navigation system, and our results were in agreement with previous studies demonstrating high reliability in TMS mapping parameters with smaller numbers of MEPs, both with (Ngomo et al., 2012) and without (Christie et al., 2007) the use of a navigation system.

4.2.1. Intra-session reliability

The agreement and high value of ICCs for measurements of pre- and post-MEPs with both short and long IPIs in FDI muscles indicate high within-session reliability. Although the intra-session reliability of MEP size at different IPIs has not been investigated before, our findings of intra-session reliability are in agreement with studies reporting high levels of reliability of MEP amplitude derived from the abductor digiti minimi (ICC of 0.97) (Christie et al., 2007), erector carpi radialis (ICC of 0.93) and FDI (ICC of 0.97) (Bastani and Jaberzadeh 2012). We also hypothesized that longer IPIs have higher level of ICCs, but the results of current study did not support this hypothesis. Our result indicates that both short and long IPIs have high level of reliability. These results support other studies in which a high reliability of MEP amplitude was detected in upper arm muscles (Kamen, 2004; Christie et al., 2007).

4.2.2. Inter-session reliability

Inter-session reliability of MEPs in FDI was high for both short and long IPIs. Although no previous researchers have investigated the effect of different IPIs on inter-session MEP reliability, the ICCs obtained in our experiment are larger than those reported by Kamen (Kamen 2004) for the FDI muscle (0.60–0.81) and Christie et al., (Christie et al., 2007) for the abductor digiti minimi (ADM) muscle (0.65–0.83). In addition, the range of ICCs in our study was similar to those reported by Bastani et al., (2012) with the same number of TMS stimuli (15 per time point) for the FDI (0.93–0.99) and Extensor carpi radialis (ECR) (0.97–0.99) muscles. Our results

demonstrate that MEP amplitude remains constant with both short and long IPIs in healthy subjects, even with an average of 48 hours between testing sessions.

Our finding has substantial implications for TMS application. It is recommended to add IPI length to the international checklist of considerations for TMS application (Chipchase et al., 2012) as an MEP modulatory criterion. Reporting the IPI may be important because our results suggest that length of IPI is a strong confounding variable in TMS studies.

The size of TMS-induced MEPs has been used as an index of CSE in neurophysiological and neurological studies (Nitsche and Paulus, 2000b). IPI length was not reported in the cited studies or in many other studies which used TMS in assessment of CSE; therefore, the results of these studies should be considered cautiously.

4.3. Limitations

It should be noted that, while some studies suggested that neuro-navigational systems provide more robust data compared to detection of hot spots by conventional method, others demonstrated that there is no significant differences between these two methods. Current study utilized the conventional method and therefore interpretation of data should be considered accordingly. Furthermore, since we studied a small group of healthy young participants, findings cannot be extrapolated to older and/or patient groups. We only evaluated one intensity (120% RMT) in a relaxed muscle, so our findings might not hold true for higher or lower intensities or active muscles. In addition, we used only the figure-of-eight magnetic coil to collect data; different results could be obtained using circular coil.

4.4. Suggestions for future research

Our work indicates that a 10 second IPI induces larger MEPs than a four-second interval with the same level of reliability. An obvious future research direction is to test a wider range of IPIs with different TMS stimulus intensities. It is also important to test the reported effects while the target muscles are active. Finally, given that rCBF changes with age and due to disease, the effects of different IPIs on elderly people and patients with different health conditions should be investigated.

To our knowledge this is the first study to investigate the effects of short and long IPIs on MEP size. The present study revealed that there is a positive relationship between the length of IPIs and the size of evoked MEPs.

The results also indicate high reliability in the size of MEPs under both short and long IPIs.

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