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The estimation of short intra-cortical inhibition depends on the proportion of spinal motoneurones activated by corticospinal inputs

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ABSTRACT

Objective: The high variability of SICI limits its utility and by extension that of TMS in clinical neurophysiology. Non-linear summation of descending volleys due to heterogeneous motoneurone properties, on which MEP size depends, has not previously been implicated as an issue in SICI evaluation.
Methods: MEP size and SICI were normalised to the test MEP (mV), and as a percentage of M_{max} to take account of the proportion of motoneurone pool activated by TMS. Two EMG systems, producing large and small MEPs, were used to determine how the normalisation affected MEPs of different amplitude.
Results: M_{max} normalisation (i) counteracted the influence of recording conditions on the MEP size, (ii) revealed a significant influence of the test size on SICI (between medium and large MEPs), and of test size on the conditioning intensity (the larger the MEP, the stronger the SICI), and (iii) decreased the variability.
Conclusions: Data normalised to M_{max} better reflect the motoneurone recruitment after SICI. To enhance reproducibility, MEP should be normalised to M_{max}. This adjusts for some of the non-linear properties at the spinal, and possibly, at cortical levels.
Significance: To reduce variability is important because TMS is becoming widely adopted and is being used in patients.

1. Introduction

Numerous experimental paradigms with transcranial magnetic stimulation (TMS) have been developed to assess cortical excitability in humans (Reis et al., 2008). In the paired pulse paradigm (Kujirai et al., 1993), the first conditioning TMS pulse is adjusted to modify motor cortex excitability, and this then influences the transsynaptic response of the pyramidal cells to the second test pulse. The conditioned motor evoked potential (MEP) is compared to the test MEP evoked by single test pulse, to investigate the excitability of inhibitory and excitatory cortical pathways. Over the past two decades, this paradigm has been extensively used, but the great variability of the data strongly limits the reliability of this technique in understanding the physiology and the pathophysiology of human motor control (Orth et al., 2003).

Stimulus parameters such as the coil location, the interval between pulses, and their intensity greatly influence the results. For instance, intra-cortical inhibition is stronger when the coil is oriented to produce postero-anterior (PA) currents in the cortex (Nakamura et al., 1997; Hanajima et al., 1998), when the time interval between the two TMS pulses is ~2 ms (short-interval intra-cortical inhibition, SICI), and when the intensity of the conditioning and test pulse are below and above the MEP threshold, respectively (Ilić et al., 2002). The threshold intensities of the conditioning pulse to activate the inhibitory and excitatory pathways are, respectively, ~60% and 80% the MEP threshold (Ilić et al., 2002), and their ratio is rather consistent (Orth et al., 2003). Clearly MEP size and the TMS intensity are correlated (Devanne et al., 1997), but with great inter-individual variability (Wassermann, 2002), which raised the question whether the test pulse should be adjusted to a specific MEP size or as a multiple of its threshold intensity. Similar modulations in SICI have been observed when the test MEP was less than 1 mV (Roshan et al., 2003; Daskalakis et al., 2004), and when the test pulse intensity was between 100% and 130% the MEP threshold (Kang et al., 2007; Garry and Thomson, 2009), but not when the test MEP was larger or the test stimulus stronger. These parameters (PA current, conditioning and test pulses, respectively, 70–80% and 120%, or 1-mV test MEP) correspond to the paradigm used in most of the studies.

SICI is commonly evaluated with the MEP ratio, and the test MEP size is expressed in mV. However, the recording conditions

Abbreviations: SICI, short-interval intra-cortical inhibition; TMS, transcranial magnetic stimulation; MEP, motor evoked potential; M_{max}, maximal motor response.

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strongly influence the EMG signals (De Luca, 2008), which can bias the inter- and intra-individual comparisons when using the raw EMG data. It is therefore advisable to normalise the EMG activity (Finsterer, 2001). In spinal neurophysiology, the H-reflex is normalised to the maximal motor response (M_{max}), which reflects the maximal compound action muscle potential when all the motor axons to the target muscle are activated simultaneously by peripheral nerve stimulation. Normalisation to M_{max} ensures that the test response size is similar in all subjects whatever the recording conditions, and that the test stimulation activates the same proportion of spinal motoneurones, limiting the influence of the non-linear input/output properties of the pool (Kernell and Hultborn, 1990), which might otherwise influence the effects of conditioning stimuli (Crone et al., 1990). While SICI may be a purely cortical phenomenon, its estimation is based on a discharge of spinal motoneurones, and the generation of a compound muscle action potential (i.e., the MEP). Moreover, the distribution of the corticospinal inputs onto the motoneurone pool is not linear (Henneman and Mendell, 1981; Bawa and Lemon, 1993; Devanne et al., 1997; Awiszus and Feistner, 1994).

We therefore addressed the question whether the recording conditions and the motoneurone recruitment can bias SICI evaluation, and contribute to the inter- and intra-subject variability. Apart from their methodological implications, the results provide further insight into the skewed distribution of corticospinal inputs at spinal level, and raise the possibility of non-linear summation at cortical level as well.

2. Methods

The experiments were carried out in 16 healthy volunteers (mean age 34.7 ± 3.5 years; 7 women; 14 right-handed) who all gave written informed consent to the experimental procedures. The study was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki), and was approved by the Local Ethics Committees of the Pitié-Salpêtrière Hospital.

2.1. Recordings

The subjects rested in a comfortable reclining armchair with head support. Bipolar surface electrodes were placed over the muscle belly of the First Dorsal Interosseous (FDI) and Abductor Digiti Minimi (ADM), on the dominant side. The electromyographic (EMG) activity was collected using two calibrated EMG systems to simulate the great variability in EMG recordings between subjects, partly due to recording conditions (see Section 4; Finsterer, 2001; De Luca, 2008). Two reliable EMG systems with different characteristics were chosen specifically because they produce reliable EMG signals of very different amplitude: the ZeroWire (ZW) EMG system (Aurion Srl, Milan, Italy; 10–1000 Hz bandwidth; Ag/AgCl electrodes PG10S, $\sim 10^4$ kΩ impedance), and the Bagnoli Desktop (BD) EMG system (Delsys, Inc., Boston, MA, US; 20–450 Hz bandwidth; Ag electrodes DE-2.1, $>10^{12}$ kΩ impedance, an extremely high value verified by the manufacturer). In addition, due to their shape (two 10 mm × 1 mm diameter bars for the BD system, and 1.5 cm diameter circular gel electrodes for the ZW system), the distance between electrodes was greater for the ZW (2–2.5 cm) than for the BD system (1 cm), and their orientation relative to the muscle fibres was different. The EMG activity was similarly amplified (1000×) with both systems, and digitally stored (2-kHz sampling rate) on a personal computer for later off-line analysis (Notocord-hem 3.4; Notocord SA, Croissy ^{s}/Seine, France). The experiments were performed in resting subjects, and EMG silence was monitored with an oscilloscope.

2.2. Stimulations

2.2.1. Peripheral nerve stimulation

Rectangular electrical pulses (1-ms duration) were delivered through bipolar surface electrodes placed in a groove on the posterior aspect of the medial epicondyle of the humerus to activate ulnar nerve motor axons to assess M_{max} in FDI and ADM. At this stimulation site, M_{max} was clearly distinct from the stimulus artifact. M_{max} and MEPs were recorded through the same electrodes (same location) with each EMG system.

2.2.2. Cortical stimulation

TMS was delivered through a figure-of-eight coil (70 mm) generating PA currents in the primary motor cortex, at the optimal site (hot spot) to evoke a MEP in the contralateral FDI EMG. The coil was connected to a Magstim Rapid unit to study MEP recruitment curves and to a Bistim module combining two Magstim 200 stimulators to provide paired pulses at a 2-ms interval through the same coil to study SICI (Magstim Company Ltd., Whitland, UK; Kujirai et al., 1993). The Magstim Rapid and Magstim 200 deliver, respectively, biphasic and monophasic waveforms, and this influences the MEP threshold and the nature of the corticospinal volley (Di Lazzaro et al., 2001). However, the two stimulators were used for different protocols, and the MEP threshold was estimated at the beginning of each experiment, for each stimulating system. The optimal coil position was marked on the scalp in all experiments, and for protocols 1 and 3 (see below), TMS was assisted by the Nexstim Navigated Brain Stimulation (NBS) system (Helsinki, Finland) using a standard MRI brain scan of each individual (www.nexstim.com). The NBS system uses a sophisticated algorithm to predict the actual location of the stimulating electric field in the cortex, and to keep it constant throughout the experiment.

2.3. Experimental protocols

2.3.1. Protocol 1: Technical sources of variability in MEP size

This protocol was designed to simulate the EMG activity collected under different recording conditions and to determine their influence on MEP size. Magstim Rapid (0.6-Hz stimulating rate) was used to compare the MEP recruitment curves in FDI when using the BD and the ZW system in six subjects: recordings started with the BD system in three subjects, or with the ZW in three other subjects (randomly determined). The hot spot for FDI was set at the beginning of the experiment, and TMS was applied at this point throughout the experiment controlled by the NBS system. TMS output was then tested to determine the resting motor threshold (RMT), corresponding to the lowest intensity for evoking a MEP of ~50 μV in at least 50% trials. Afterwards, TMS intensity was randomly changed from MEP threshold to that for the maximal MEP; 20 stimuli were delivered at each intensity. When the MEP recruitment curve was obtained with the first EMG system, the ulnar nerve was stimulated to measure M_{max} with this system, and then again with the second EMG system before starting the MEP recruitment curve with that EMG system; attention was paid to ensure that the electrodes of the two systems were at about the same location over the muscle belly.

2.3.2. Protocol 2: Technical and within-subject sources of variability in SICI

The hot spot for FDI and the RMT were determined at the beginning of each experiment. The paired pulse paradigm consisted of delivering two stimuli at a 2-ms interval through the same coil to evoke SICI (Kujirai et al., 1993). The first (conditioning) pulse was sub-threshold for evoking a MEP, as confirmed in the averaged EMG ($N = 15$). The second (test) pulse was supra-threshold, and its intensity was randomly changed from one session to another in or-