Are ipsilateral motor evoked potentials subject to intracortical inhibition?

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Abstract (250 words)

Paired-pulse transcranial magnetic stimulation (TMS) can be used to examine intracortical inhibition in primary motor cortex (M1), termed short-interval intracortical inhibition (SICI). To our knowledge, SICI has only been demonstrated in contralateral motor evoked potentials (MEPs). Ipsilateral MEPs (iMEPs) are assumed to reflect excitability of an uncrossed oligosynaptic pathway, and can sometimes be evoked in proximal upper-limb muscles using high intensity TMS. We examined whether iMEPs in the *Biceps Brachii* (BB) would be suppressed by sub-threshold conditioning, therefore demonstrating SICI of iMEPs. TMS was delivered to the dominant M1 to evoke conditioned (C) and non-conditioned (NC) iMEPs in the non-dominant BB of healthy participants during weak bilateral elbow flexion. The conditioning stimulus intensities tested were 85%, 100% and 115% of active motor threshold (AMT), at 2 ms and 4 ms interstimulus intervals (ISI). The iMEP ratio (C/NC) was calculated for each condition to assess the amount of inhibition. Inhibition of iMEPs was present at 2 ms ISI with 100% and 115% AMT (both $P < 0.03$), mediated by a reduction in persistence and size (all $P < 0.05$). To our knowledge this is the first demonstration of SICI of iMEPs. This technique may be useful as a tool to better understand the role of ipsilateral M1 during functional motor tasks.

Introduction

The cortical control of ipsilateral proximal upper limb muscles is rarely studied in healthy people. This is surprising given that ipsilateral control of the upper limb is evident after adult stroke (e.g., Verstynen et al. (2005), Ward et al. (2006), Schwerin et al. (2008)) and cerebral palsy (e.g., Eyre et al. (2007), Eyre et al. (2001)). Further, the role of intracortical inhibition in control of the ipsilateral proximal upper limb is not well understood. Exploring new paradigms to probe intracortical inhibitory circuits in the ipsilateral primary motor cortex (M1) may help elucidate the role of ipsilateral M1 during upper limb movement.

Short-interval paired-pulse transcranial magnetic stimulation (TMS) is an established non-invasive measure of intracortical inhibition in M1. Typically, short-interval intracortical inhibition (SICI) is performed by delivering a subthreshold conditioning stimulus (CS), followed 1-5 ms later by a suprathreshold test stimulus (TS) to elicit motor evoked potentials (MEPs) in muscles of the contralateral upper limb. The suppressive effect of conditioning is thought to be mediated by gamma-aminobutyric acid (GABA) synaptic activity via $GABA_A$-mediated receptors as SICI is enhanced by allosteric $GABA_A$ receptor modulators (Ziemann et al. 1996a; Ziemann et al. 1996b). To our knowledge, no study has examined the effect of short-interval paired-pulse TMS on ipsilateral MEPs. Evidence of MEP suppression from such a technique could yield new insights into the functional role of the ipsilateral M1 for upper limb control.

Ipsilateral MEPs (iMEPs) can be evoked in many individuals with high intensity TMS applied over M1 and pre-activation of the ipsilateral musculature (Tazoe and Perez 2014; Ziemann et al. 1999). Ipsilateral MEPs are thought to reflect excitability of an uncrossed oligosynaptic pathway, such as the cortico-reticulospinal or cortico-propriospinal pathway

(Ziemann et al. 1999). They are characterized by a long latency and high threshold, are more likely found in proximal muscles (Bawa et al. 2004), and can be modulated by the type of task contraction (Tazoe and Perez 2014), neck rotation (Tazoe and Perez 2014; Ziemann et al. 1999), and non-invasive brain stimulation (Bradnam et al. 2010). Ipsilateral MEPs have been observed in a patient with complete agenesis of the corpus callosum (Ziemann et al. 1999), and are up-regulated at the chronic stage after stroke proportional to the severity of upper limb impairment (Schwerin et al. 2008).

Another protocol presumed to assess putative intracortical inhibition in M1 is the use of subthreshold TMS during tonic isometric muscle contraction, and averaging over many trials (Davey et al. 1994). Using this technique subthreshold TMS over ipsilateral M1 exhibited more EMG suppression in the ipsilateral *biceps brachii* (BB) during bilateral elbow flexion than unilateral elbow flexion (Tazoe and Perez 2014). Therefore, we used bilateral elbow flexion as the motor task in this experiment. Our hypothesis was that iMEPs in the BB would be suppressed by subthreshold conditioning at ISIs known to produce SICI of contralateral MEPs (cMEPs). Based on previous studies with cMEPs, we hypothesized that a 2 ms interstimulus interval (ISI) would induce more suppression of iMEPs than a longer ISI, and more suppression would be observed with stronger CS intensities (Chen et al. 1998; Peurala et al. 2008).

Methods

Participants

In total, twenty-five adults were initially screened for the presence of iMEPs in the non-dominant BB. Ten neurologically healthy adults (mean age 25.1 yrs, range 20 – 31 yrs, 4

89 males, 1 left-handed) met the study criteria. Participants were included if they produced
90 iMEPs in > 50% of trials with single-pulse TMS, and inhibition or facilitation with paired-
91 pulse TMS. All participants gave written informed consent, and the local ethics committee
92 approved the study in accordance with the Declaration of Helsinki. Participants were assessed
93 for contraindications to TMS by a neurologist, and handedness was assessed with the
94 Edinburgh Handedness Inventory (Oldfield 1971).

95 *Electromyography*

96 Surface electromyography (EMG) was recorded from the short head of left and right
97 BB using disposable electrodes (Ambu Blue Sensor Paediatric NS, Denmark) placed over the
98 muscle bellies 2.5 cm apart. Standard skin preparation procedures were used. EMG signals
99 were amplified (CED 1902; Cambridge Electronic Design, United Kingdom), band-pass
100 filtered (10–1000 Hz), and sampled at 2 kHz (CED 1401).

101 *Task position*

102 Participants were seated with shoulders neutral, both forearms supinated and elbows
103 resting on a firm surface. A cuff was secured around each wrist, attached to metal rods
104 embedded with force transducers. All participants performed 2 – 3 maximal isometric elbow
105 flexion contractions with both arms together for 3 – 5 seconds. The force was recorded using
106 PowerLab and LabChart software (ADinstruments, New Zealand). For the remainder of the
107 experiment participants held bilateral elbow flexion at 10% of their maximum voluntary
108 contraction (MVC) and targets were displayed on a screen to encourage accurate task
109 performance.

110 *Transcranial Magnetic Stimulation*

TMS was delivered to dominant M1 using a figure-of-eight D70^2 coil and two Magstim Model 200 stimulators connected to a BiStim unit (Magstim Company, United Kingdom). The coil was held tangential to the scalp, with cortical current directed posterior to anterior (Bradnam et al. 2011; Tazoe and Perez 2014) and the optimal site for eliciting cMEPs in the dominant BB was marked on the scalp. Active motor threshold (AMT) in the contralateral BB was defined as the minimum stimulus intensity to evoke a 200 μV cMEP in four out of eight trials during bilateral elbow flexion at 10% MVC (mean AMT = 36.9% maximum stimulator output (MSO), range 28 – 47% MSO).

To determine if an individual produced acceptable iMEPs, 12 stimuli at 100% MSO were delivered to the dominant M1 during bilateral elbow flexion at 10% MVC. Rest breaks were given every 4 stimuli. Ipsilateral MEPs were identified from the average rectified EMG trace of the non-dominant BB. An iMEP was deemed acceptable when the EMG from the waveform average exceeded the mean background EMG (BG) + 1 standard deviation (SD) for at least 5 ms (Ziemann et al. 1999).

For paired-pulse TMS, the test stimulus (TS) intensity was determined by delivering blocks of 12 stimuli at decreasing intervals of 5 – 10% MSO from maximum, until an iMEP was no longer deemed acceptable from the waveform average. The TS was the lowest intensity that produced sizeable (> 100 μV·ms) and persistent (>50%) iMEPs. The conditioning stimulus (CS) intensities were 85%, 100% and 115% of the contralateral BB AMT (termed CS_{85}, CS_{100}, CS_{115}). Non-conditioned (NC) trials delivered the TS only. Conditioned (C) trials delivered a CS before the TS, with an interstimulus interval (ISI) of 2 ms or 4 ms. Twenty-four NC trials and 12 C trials for each condition were collected in a randomised order at 0.2 Hz, with rest breaks every 6 stimuli.

Data processing

Ipsilateral MEPs were measured from rectified EMG for the non-dominant BB. The iMEP onset and offset was determined from the averaged waveform trace at 100% MSO and was used as the individualised iMEP window for each participant. The onset was the earliest deflection of the EMG that was maintained above the BG mean + 1 SD for at least 5 ms. The offset was the first instance the EMG returned to the BG mean + 1 SD. From each trace, iMEPs were measured as the area within the iMEP window, less an equivalent window of BG EMG area; iMEP (μV·ms) = iMEP area – BG area.

Persistence of iMEPs was calculated as the number of trials the iMEP was > 100 μV·ms out of the total for each condition. A threshold of 100 μV·ms was chosen on the basis that it provides an objective criterion to exclude trials where an iMEP is not present. Previous studies have relied on visual inspection of the trace (Schwerin et al. 2008; Schwerin et al. 2011). The iMEP latency was obtained from trials where the iMEP was > 100 μV·ms. The iMEP latency was measured from the raw EMG as the first prominent deflection of the EMG within a pre-determined iMEP window (i.e., 3 - 15 ms later than the cMEP latency).

The cMEP latency was measured from the raw EMG as the first deflection at least 8 ms after TMS. Contralateral MEPs were measured by calculating the integral of rectified EMG for the dominant BB. The cMEP area was calculated in a 20 ms window from the cMEP latency (mean = 10.1 ms, range 9.0 – 11.5 ms), and expressed as the difference between the cMEP area and an equivalent window (i.e., 20 ms) of background EMG; cMEP (μV·ms) = iMEP area – BG area.

The root mean square of the EMG (rmsEMG) was calculated for 90 ms before the stimulus artefact in the ipsilateral and contralateral BB to ensure background EMG activity was equivalent between conditions.

Statistical analysis

The iMEP and cMEP ratios were calculated (C/NC) for each condition. The iMEP ratio was an average of all trials per condition, and the iMEP+ ratio was an average of trials where the iMEP was > 100 μV·ms. One-sample t-tests of the iMEP and cMEP ratios were used to detect differences from 1. Delta (Δ) iMEP persistence was calculated as the difference between C and NC iMEP persistence (Δ persistence = C – NC). The iMEP ratio, iMEP+ ratio, cMEP ratio, Δ persistence, and iMEP latency were analysed with a 2 ISI (2 ms, 4 ms) x 3 CS intensity (CS_{85}, CS_{100}, CS_{115}) repeated measures analysis of variance (rmANOVA). Paired t-tests between the NC iMEP latency and C iMEP latency for each condition were also performed. The rmsEMG for the ipsilateral and contralateral BB were analysed in separate one-way ANOVAs.

Effects were deemed significant if $P < 0.05$ and post-hoc tests were conducted using paired and one-sample t-tests. For multiple pairwise comparisons a modified Bonferroni procedure was used (Rom 1990). Means ± standard error (SE) are reported in the text.

Results

The main result is shown in Figure 2A. One-sample t-tests of the iMEP ratios confirmed that iMEPs were suppressed with an ISI of 2 ms with CS_{100} (0.65 ± 0.14; $t_9 = -2.53$, $P = 0.03$) and CS_{115} (0.64 ± 0.11; $t_9 = -3.44$, $P = 0.007$), but not CS_{85} (0.85 ± 0.13; $t_9 = -1.12$, $P = 0.29$). There was no iMEP suppression at 4 ms with any conditioning intensity (CS_{85}: 1.30 ± 0.26; $t_9 = 1.17$, $P = 0.27$; CS_{100}: 1.05 ± 0.15; $t_9 = 0.35$, $P = 0.74$) although there was a non-significant trend with CS_{115} (0.72 ± 0.14; $t_9 = -2.06$, $P = 0.07$). ANOVA indicated a main effect of ISI ($F_{1,9} = 9.52$, $P = 0.01$) and CS intensity ($F_{2,18} = 6.72$, $P = 0.01$), and no interaction ($F_{2,18} = 1.30$, $P > 0.30$). Suppression was greater with 2 ms ISI compared to 4 ms ISI (2 ms = 0.71 ± 0.10; 4 ms 1.02 ± 0.15). Post-hoc analyses revealed more iMEP

suppression at CS_{115} than CS_{85} ($P = 0.02$), but there were no differences between CS_{85} and CS_{100} ($P = 0.10$), or CS_{100} and CS_{115}, ($P = 0.14$) [$CS_{85} = 1.08 \pm 0.17$; $CS_{100} = 0.85 \pm 0.12$; $CS_{115} = 0.68 \pm 0.10$].

The persistence of iMEPs was 74.1 ± 5.6% (Figure 2B). For ΔiMEP persistence there was a main effect of ISI ($F_{1,9} = 5.85$, $P = 0.04$) and a non-significant trend for CS ($F_{2,18} = 2.79$, $P = 0.09$) and no ISI x CS interaction ($F_{2,18} = 0.32$, $P = 0.73$) (Figure 2C). ΔiMEP persistence was less at 2 ms than 4 ms (2 ms = -7.5 ± 5.7%; 4 ms = -1.6 ± 5.7%; Figure 2C) and one-sample t-tests confirmed lower ΔiMEP persistence at 2 ms ($t_{29} = -2.13$, $P = 0.04$) but not 4 ms ($t_{29} = -0.45$, $P = 0.66$).

Analysis of iMEP+ ratio included only trials where an iMEP was > 100 μV·ms. The pattern of results was similar to that above. iMEP+ ratios were suppressed at 2 ms with CS_{100} (0.81 ± 0.08; $t_9 = -2.27$, $P = 0.049$) and a non-significant trends with CS_{115} at 2 ms (0.80 ± 0.09; $t_9 = -2.09$, $P = 0.066$) and 4 ms (0.83 ± 0.09; $t_9 = -1.84$, $P = 0.099$) (all other $P > 0.16$; Figure 2D). There was a main effect of CS intensity ($F_{2,18} = 4.88$, $P = 0.02$) and no other main effects or interactions (all $P > 0.12$). The iMEP+ ratio at at CS85 showed less suppression than at CS_{100} ($P = 0.048$) or CS_{115} ($P = 0.02$), with no difference between them [$CS_{85} = 1.10 \pm 0.08$; $CS_{100} = 0.94 \pm 0.07$; $CS_{115} = 0.82 \pm 0.09$].

iMEP latency was consistent across conditions and compared to NC (all $P > 0.30$). The average iMEP latency was 18.81 ± 0.29 ms, which was 8.72 ± 1.89 ms later than the cMEP latency.

As expected cMEPs were suppressed at ISI of 2 ms with CS_{100} (0.77 ± 0.06; $t_9 = -3.69$, $P = 0.005$) and CS_{115} (0.76 ± 0.09; $t_9 = -2.75$, $P = 0.022$) and ISI of 4 ms with CS_{100} and CS_{115} (100% AMT: 0.78 ± 0.05; $t_9 = -4.85$, $P = 0.001$, 115% AMT: 0.71 ± 0.06; $t_9 = -5.03$, $P = 0.001$, Figure 3A). There was also a non-significant trend for inhibition at 2 ms with CS_{85}

(0.92 ± 0.05; t_9 = -1.85, P = 0.097). There was a main effect of CS intensity ($F_{2,18}$ = 9.32, P = 0.002) and no other main effects or interactions (all P > 0.70). The cMEP ratio at CS_{85} was higher than CS_{100} and CS_{115} (both P < 0.01), and there was no difference between CS_{100} and CS_{115} (P = 0.38) [CS_{85} = 0.92 ± 0.02; CS_{100} = 0.78 ± 0.04; CS_{115} = 0.73 ± 0.06]. For comparison, Figure 3B depicts the iMEP and cMEP ratios of all participants.

The pretrigger rmsEMG was consistent across conditions for the ipsilateral and contralateral BB (all P > 0.998).

Discussion

To our knowledge this is the first demonstration of iMEP suppression using short-interval paired-pulse TMS. Suppression of iMEPs occurred via reduced iMEP persistence and size. Suppression of cMEPs also occurred at the same ISIs which are known to elicit SICI of cMEPs, a $GABA_A$-receptor mediated inhibitory process. There is a growing body of evidence suggesting a role of ipsilateral M1 during skilled upper limb movement in healthy individuals (Diedrichsen et al. 2013; McCambridge et al. 2011; Uehara and Funase 2014; Verstynen et al. 2005) and those affected by stroke (Bradnam et al. 2013; Riecker et al. 2010; Ward et al. 2006). Short-interval paired-pulse TMS of iMEPs could be useful for understanding how intracortical inhibitory circuits that act on ipsilateral motor pathways are modulated during functional motor tasks.

In the present study, 10 of 25 participants produced acceptable iMEPs based on established criteria (Ziemann et al. 1999). This is a low to moderate proportion of responders compared to other studies targeting iMEPs in the BB (Bradnam et al. 2010; McCambridge et al. 2011; McCambridge et al. 2014; Tazoe and Perez 2014; Ziemann et al. 1999). One reason

for this low proportion may have been the relatively weak task contraction compared to previous studies (Tazoe and Perez 2014; Ziemann et al. 1999). However, given that intracortical inhibition is down-regulated with voluntary contraction (Reynolds and Ashby 1999; Roshan et al. 2003), our aim was to limit the contraction strength to 10% MVC in order to determine if sub-threshold conditioning would suppress iMEPs. The low proportion of responders is therefore likely reflective of the weaker contraction, and not indicative of less reliance on ipsilateral control of the upper limb.

Ipsilateral MEPs were present in 74% of trials overall, with a latency of 18.8 ± 0.2 ms which is consistent with other studies in the BB (Bradnam et al. 2010; Lewis and Perreault 2007; McCambridge et al. 2011; McCambridge et al. 2014; Tazoe and Perez 2014). Paired-pulse TMS suppressed iMEPs with an ISI of 2 ms at stronger CS intensities (CS_{100} and CS_{115}, Figure 2A). The persistence of iMEPs was reduced by 7.5% at 2 ms ISI (Figure 2C). Of the trials where an iMEP was present (i.e., iMEP+ ratio included only iMEPs > 100 μV·ms), the suppressive effect of paired-pulse TMS with 2 ms at CS_{100} was still evident (Figure 2D). Therefore suppression of iMEPs was mediated by both reduced iMEP persistence and size.

In the present study, cMEPs were suppressed by both ISI's with stronger CS intensities (CS_{100} and CS_{115}, Figure 3A). In general, short-interval paired-pulse TMS similarly modulated contralateral and ipsilateral MEPs across each condition. The main contrast between conditions was seen at 4 ms with CS_{100}, where suppression was found for cMEPs but not iMEPs. One reason for this could relate to differences in the threshold of ipsilateral vs contralateral pathways (Bawa et al. 2004; Ziemann et al. 1999), as a slightly higher CS intensity (i.e., CS_{115} at 4 ms) did produce iMEP suppression. Alternatively, it could relate to inter-individual variability, as iMEP ratios appeared to be more variable than cMEP ratios (Figure 3B). A limitation of the study was that the TMS hotspot was not optimised for iMEPs, therefore this could have influenced iMEP variability. Because paired-pulse TMS

suppressed both contralateral and ipsilateral motor pathways at known ISIs and CS intensities for SICI, we speculate these effects reflect intracortical inhibition in M1 whereby subthreshold conditioning activated intracortical interneurons that inhibited pyramidal neurons of both motor pathways.

As far as we know this is the first report of intracortical inhibition of ipsilateral motor evoked potentials. There are several possible avenues for future neurophysiological investigations. Pharmacological studies could specifically determine whether the observed suppression of iMEPs is dependent on a particular $GABA_A$-receptor subunit (e.g., Di Lazzaro et al. (2006)). Another question is how pyramidal neurons in M1 are influenced by both facilitatory and inhibitory networks. For example, supra-threshold paired-pulse TMS can facilitate iMEPs in both healthy and chronic stroke participants (Schwerin et al. 2011). Ipsilateral motor pathways from contralesional M1 may be up-regulated after stroke (Caramia et al. 2000; Schwerin et al. 2008) especially when the ipsilesional corticospinal tract has been damaged (Bradnam et al. 2013; Ward et al. 2006). It remains to be determined if intracortical inhibitory networks functionally modulate ipsilateral pathways in a task-dependent manner. Such investigations may provide insight into neural re-organisation and motor recovery in conditions such as stroke or cerebral palsy.

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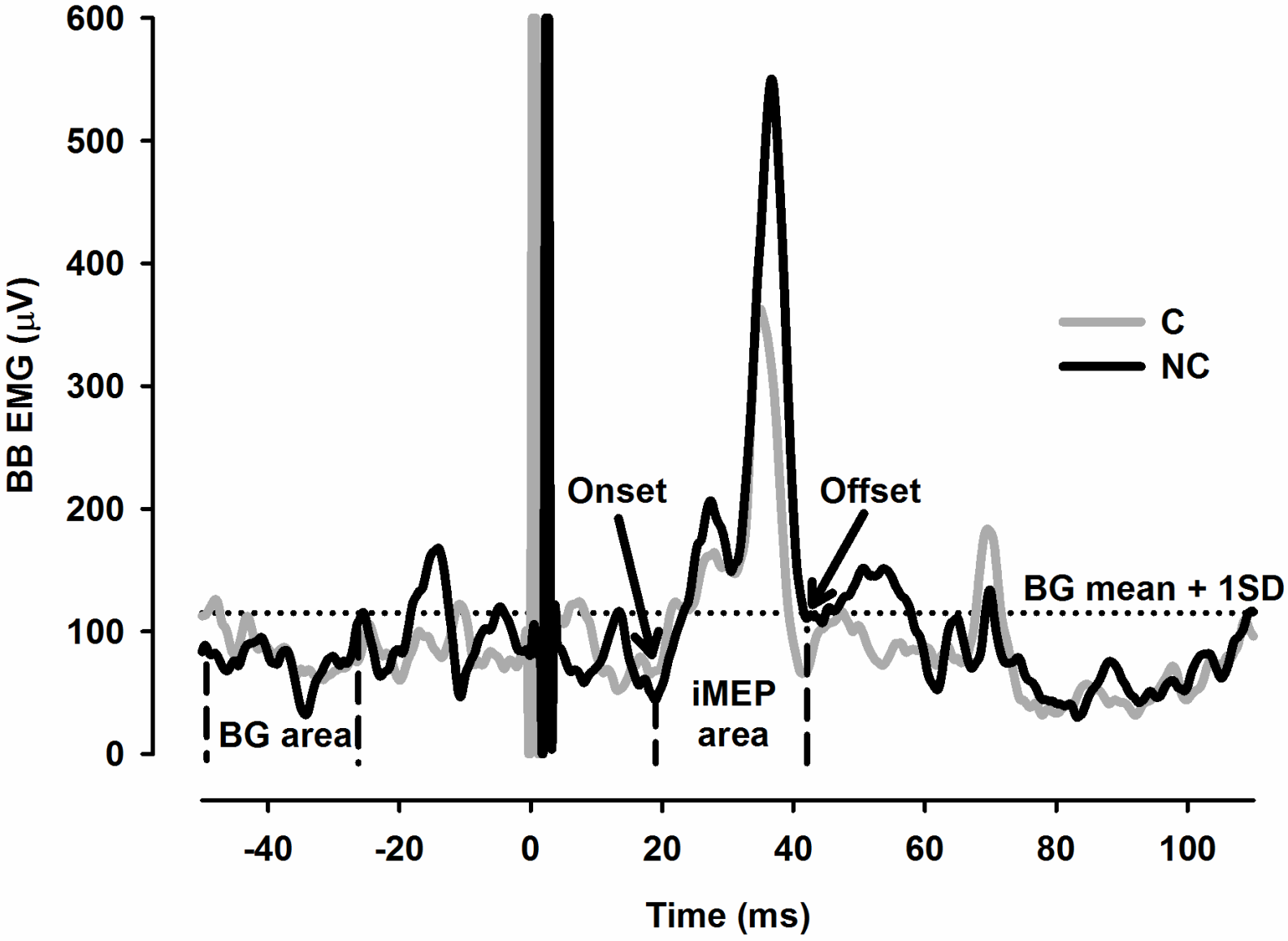
Figure 1. Average rectified EMG recordings from the ipsilateral BB of a representative participant. The non-conditioned (NC) trace is shown in black, the conditioned trace (C) at 2 ms with CS_{100} is shown in grey. The iMEP ratio was 0.42. Ipsilateral MEPs were deemed present in an individual if the EMG exceeded the mean background (BG) EMG + 1 standard deviation (SD) for > 5 ms (Ziemann et al. 1999). Ipsilateral MEPs were measured as the area between the onset and offset, less an equivalent window of BG EMG, iMEP = iMEP area – BG area.

Figure 2. Group averages (n = 10) of iMEP ratios (A, D) and iMEP persistence (B, C) for each conditioning stimulus intensity at 2 ms (black) or 4 ms (grey) interstimulus intervals (ISI). **A.** iMEP ratios included all trials. The rmANOVA revealed a main effect of ISI (P = 0.01) and CS (P = 0.01). Suppression was present at 2 ms with CS_{100} and CS_{115} (*P < 0.05) and a trend for 4 ms at CS_{115} (#P < 0.1). **B.** Persistence was calculated as the number of trials the iMEP was > 100 μV·ms out of the total number of trials. Non-conditioned (NC) iMEP persistence is shown as the open bar. **C.** ΔiMEP persistence was the difference between each condition (C) from NC. The rmANOVA revealed a main effect of ISI (P = 0.04), with persistence at 2 ms lower than 4 ms. **D.** iMEP+ ratios included trials with an iMEP > 100 μV·ms, therefore excluded trials where an iMEP was not present. Suppression of iMEPs was found at 2 ms with CS_{100} (*P < 0.05) and a trend for both ISI's at CS_{100} (#P < 0.1).

Figure 3A. Group averages (n = 10) of cMEP ratios for each conditioning stimulus (CS) intensity at 2 ms (black) or 4 ms (grey) interstimulus intervals (ISI). Inhibition was present at 2 ms and 4 ms with CS_{100} and CS_{115} (*P < 0.05) and a trend for 2 ms with CS_{85} (#P < 0.1). **B**. Dot plot of individual iMEP (circle) and cMEP (triangle) ratios for each CS intensity at 2 ms (black) and 4 ms (grey) ISIs. Each data point within a condition represents one individual.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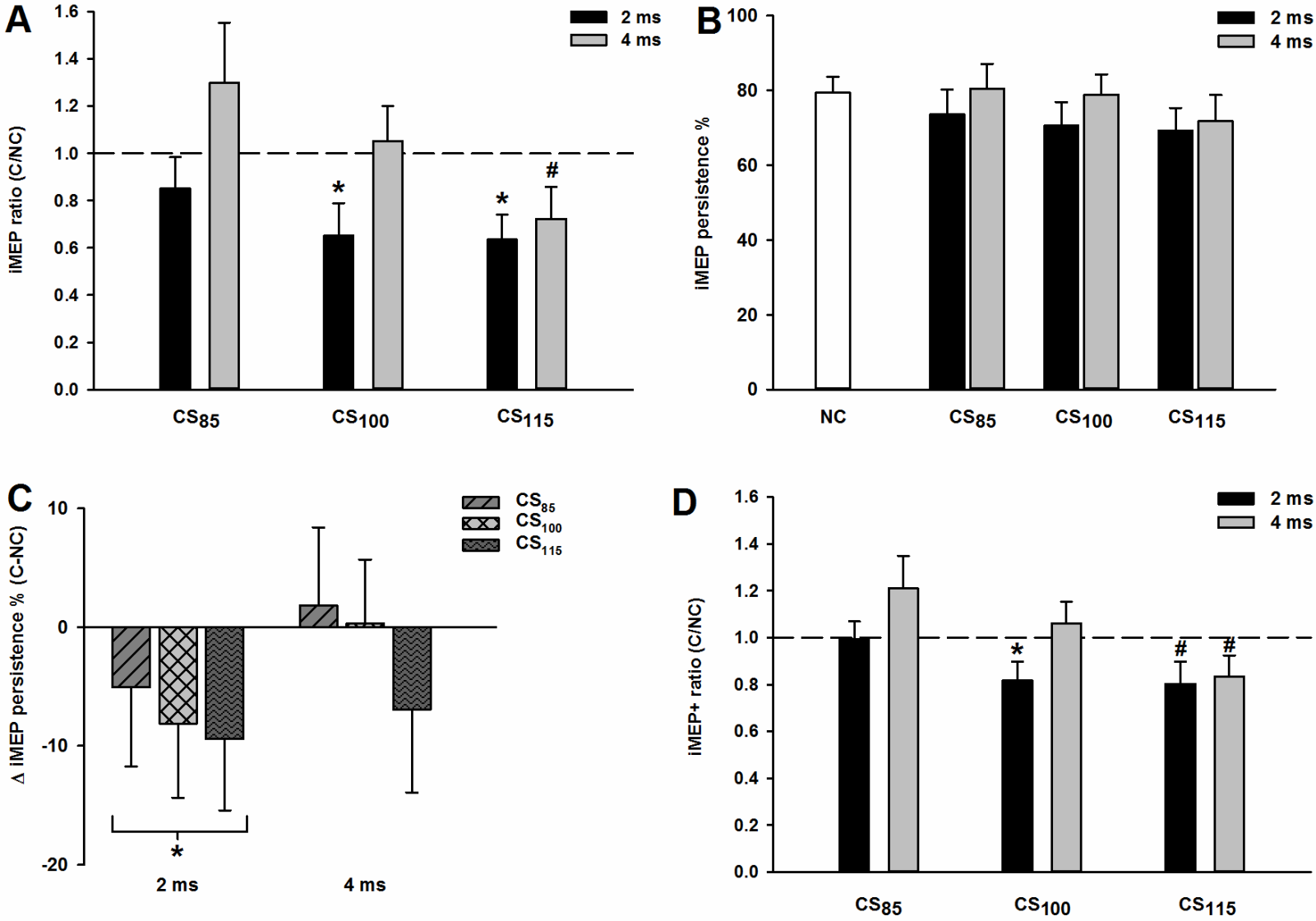
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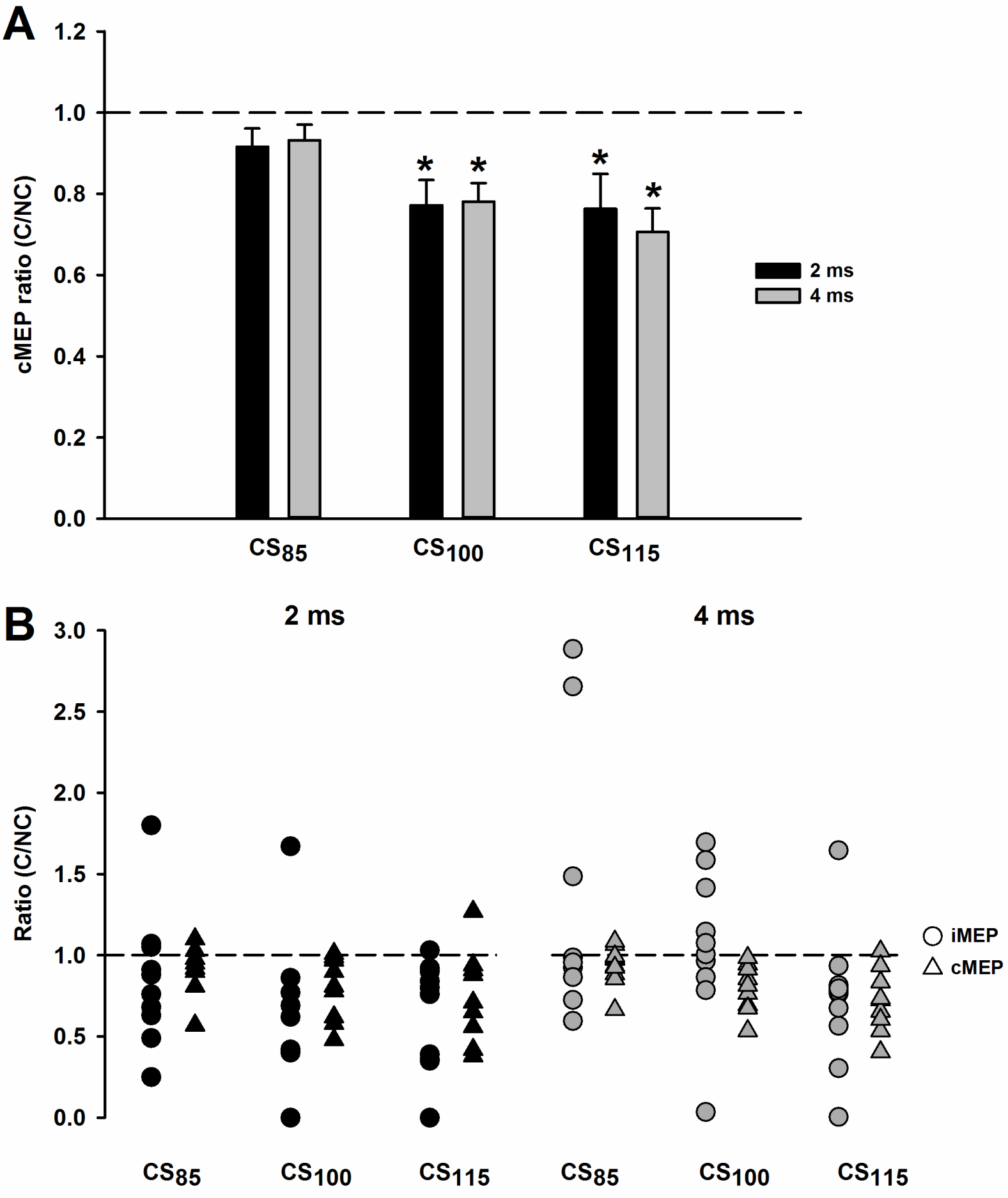
iMEP persistence %
100
80
60
40
20
0
NC
CS85
CS100
CS115
C
CS85
CS100
CS115
Δ iMEP persistence % (C-NC)
10
0
-10
-20
*
2 ms
4 ms
D
2 ms
4 ms
iMEP+ ratio (C/NC)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
#
#
CS85
CS100
CS115


A
1.2
1.0
0.8
0.6
0.4
0.2
0.0
cMEP ratio (C/NC)
*
*
*
*
2 ms
4 ms
CS85
CS100
CS115
B
2 ms
4 ms
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Ratio (C/NC)
iMEP
cMEP
CS85
CS100
CS115
CS85
CS100
CS115