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INTERHEMISPHERIC SENSORIMOTOR INTEGRATION; AN UPPER LIMB PHENOMENON?

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Abstract—Somatosensory information from the limbs reaches the contralateral Primary Sensory Cortex (S1) with a delay of 23 ms for finger, and 40 ms for leg (somatosensory N20/N40). Upon arrival of this input in the cortex, motor evoked potentials (MEPs) elicited by Transcranial Magnetic Stimulation (TMS) are momentarily inhibited. This phenomenon is called 'short latency afferent inhibition (SAI)' and can be used as a tool for investigating sensorimotor interactions in the brain. We used SAI to investigate the process of sensorimotor integration in the hemisphere *ipsilateral* to the stimulated limb. We hypothesized that ipsilateral SAI would occur with a delay following the onset of contralateral SAI, to allow for transcallosal conduction of the signal. We electrically stimulated the limb either contralateral or ipsilateral to the hemisphere receiving TMS, using a range of different interstimulus intervals (ISI). We tested the First Dorsal Interosseous (FDI) muscle in the hand, and Tibialis Anterior (TA) in the lower leg, in three separate experiments. Ipsilateral SAI was elicited in the upper limb (FDI) at all ISIs that were greater than N20 + 18 ms (all $p < .05$) but never at any earlier timepoint. No ipsilateral SAI was detected in the lower limb (TA) at any of the tested ISIs. The delayed onset timing of ipsilateral SAI suggests that transcallosal communication mediates this inhibitory process for the upper limb. The complete absence of ipsilateral SAI in the lower limb warrants consideration of the potential limb-specific differences in demands for bilateral sensorimotor integration.

Key words: inhibition, ipsilateral, sensorimotor integration, short latency afferent inhibition, somatosensory.

INTRODUCTION

Afferent somatosensory signals from the limbs provide the brain with vital knowledge required for guiding, updating and learning movements. Surprisingly, in cases where deafferentation has occurred and all ascending signals are lost, the execution of many preprogrammed finger movements requiring complex muscle synergies is still possible (Rothwell et al., 1982). However, severe deficits are noted in the capability to perform the finest motor tasks such as writing, buttoning a shirt or picking up a coin (Bossom, 1974; Rothwell et al., 1982), and in the ability to learn new motor skills (Rothwell et al., 1982; Rosenkranz and Rothwell, 2012; Choi et al., 2013). Given the importance of sensorimotor integration for motor control, it is not surprising that peripheral afferent information influences Primary Motor Cortex (M1) activity in primates via dense intracortical projections between Primary Sensory Cortex (S1) and M1 (Goldring et al., 1970). Additionally, a more direct route exists whereby afferent somatosensory signals detected by cutaneous or proprioceptive receptors of one limb are transmitted to the contralateral thalamic nucleus ventralis posterior lateralis pars oralis (VPLo) (Kievit and Kuypers, 1977; Horne and Tracey, 1979; Lemon, 1981) and from there directly to M1.

It is well established that particularly complex tasks activate motor areas of *both* hemispheres. However, it remains unknown whether somatosensory information influences M1 activity in the hemisphere *ipsilateral* to the stimulated limb and which specific neural pathways might mediate this effect.

In humans, somatosensory stimulation of the fingertip reaches contralateral S1 with a delay of ~23 ms (ms), thus generating the negative N20 potential that is detectable at the scalp using electroencephalography (EEG). Immediately following the arrival of this information to the S1, motor cortical output is briefly inhibited, a phenomenon referred to as short latency afferent inhibition (SAI) (Maertens de Noordhout et al., 1992; Tokimura et al., 2000). The duration of this inhibition has been reported up to 50 ms (Tamburin et al.,

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Abbreviations: EMG, electromyography; FDI, First Dorsal Interosseous; ISI, interstimulus interval; M1, Primary Motor Cortex; MEP, Motor Evoked Potential; PT, Perceptual Threshold; RMT, Resting Motor Threshold; S1, Primary Sensory Cortex; S2, Secondary Sensory Cortex; SAI, short latency afferent inhibition; TMS, Transcranial Magnetic Stimulation; TA, Tibialis Anterior.

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2003; Helmich et al., 2005), it occurs for both resting and active muscles (Tokimura et al., 2000), increases with greater intensity of stimulation (Wardman et al., 2014), but appears to be exclusive to electrical stimulation. Natural stimulation of muscle, joint and cutaneous receptors in the hand and forearm within a similar time frame, through e.g. passive rotation or muscle stretch, increases rather than decreases the excitability of projections to the stimulated muscle (Day et al., 1991). Measuring this process is believed to provide a readout of direct transmission of somatosensory information to M1 in humans. Although the system is measured at rest and in the absence of voluntary motor output, it is generally believed that SAI opens a window into the fundamental process of sensorimotor interactions (Tokimura et al., 2000).

Here we used SAI as a tool to investigate the process of sensorimotor integration not only in the contralateral hemisphere, but also in the hemisphere ipsilateral to the stimulated limb. We hypothesized that ipsilateral SAI would occur with a delay following the onset of contralateral SAI, to allow for transcallosal conduction of the signal. Moreover, we test whether sensorimotor integration of ipsilateral stimuli reflects a general organisational principle of the brain, or whether limb specific differences exist. For instance, the hand region of S1 contains many neurons with bilateral receptive fields, whereas those of the lower limb region are comparatively scarce (Iwamura, 2000). Thus it is possible that the neural circuits allowing sensory information to reach M1 of both hemispheres may be different between upper and lower limbs, likely due to different demands for fine sensory-guided motor control as well as for cooperative movements involving both body sides. We detected ipsilateral SAI in the upper limb (Experiment 1) but not in the lower limb (Experiment 2 & 3) and show that the earliest occurrence of ipsilateral SAI occurs ~41 ms after the somatosensory stimulus has been applied to the hand (Experiment 3).

EXPERIMENTAL PROCEDURES

Subjects

Twenty-four neurologically healthy subjects participated in Experiment 1 (16 females; mean age, 22 ± 3.7 years). All were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Twenty-three of these participated in a condition where motor evoked potentials (MEPs) were recorded from the dominant limb, 18 in a condition where MEPs were recorded from the non-dominant limb, and 17 participated in both conditions. Fifteen more subjects (4 females; mean age, 26 ± 4.4 years) participated in Experiment 2, and 20 (11 females; mean age, 24.5 ± 3.2 years) in Experiment 3. The experiments were approved by the ETH Ethics Committee as well as by the Kantonale Ethikkommission Zurich, and conform to the Declaration of Helsinki (1964).

General setup

Subjects sat in a comfortable chair with both arms and legs resting in a neutral position supported by foam pillows. MEPs were recorded from First Dorsal Interosseous (FDI) in Experiment 1 & 3, and from TA in Experiment 2 & 3, with surface electromyography (EMG; Trigno Wireless; Delsys). EMG data were sampled at 5000 Hz (CED Power 1401; Cambridge Electronic Design), amplified, band-pass filtered (30–1000 Hz), and stored on a PC for off-line analysis.

Transcranial Magnetic Stimulation (TMS) measurements

TMS was performed with a figure-of-eight coil (internal coil diameter 50 mm- Experiment 1 & 3), a custom-made 'bat wing coil' (internal diameter 70 mm-Experiment 2) or a 'double cone' coil (internal diameter 90 mm-Experiment 3), connected to a Magstim 200 stimulator (Magstim, Whitland, UK). The coil was held over the hotspot of the FDI muscle (Experiment 1 & 3) or Tibialis Anterior (TA) (Experiment 2 & 3), at the location with the largest and most consistent MEPs, and with the optimal orientation for evoking a descending volley in the corticospinal tract. Once the hotspot was established, the lowest stimulation intensity at which MEPs with peak-to-peak amplitude of approximately 50 μV were evoked in at least 5 of 10 consecutive trials was taken as Resting Motor Threshold (RMT). During the experiments (described below), the inter-trial interval was 7 s with a random jitter of 20%. The intensity was set at 120% RMT. Subjects kept eyes open with attention directed to a fixation point on a monitor in front of them, and were instructed to relax their limbs. Background muscle activation was closely monitored throughout and subjects were instructed to relax if the root mean square (rms) background EMG exceeded 10 μV.

Electrical stimulation

Electrical stimulation (Digitimer DS7A, Hertfortshire, UK) was applied to the fingertip of the right or left index finger when FDI was the target of TMS, and to the dorsal surface of the right foot when the TA was the target. More specifically, for finger stimulation the cathode was fixed on the fingertip and the anode was fixed laterally on the proximal phalanx of the index finger. For the foot, both electrodes were placed at the level of the second metatarsal, with the anode and cathode fixed approximately 5 cm and 2 cm from the toes, respectively. To ensure that the somatosensory stimulation was perceived strongly enough to elicit an ipsilateral brain response, without requiring high stimulation intensities that may activate nociceptors, we used a train of 3 consecutive pulses with a pulse width of 0.1 ms and an inter-pulse-interval of 3.4 ms was applied (i.e. 7.1 ms overall duration). For each subject, the Perceptual Threshold (PT) was defined before each block of measurements. To find the PT, the intensity was initially set above the threshold. Subjects were instructed to indicate whether they felt the triplet of pulses, which were applied every 8 s (with a variation of 20%). Intensity was decreased in 0.10-mA steps until the subject indicated that he/she was not able to feel

the pulse anymore. Next, the intensity was turned up in 0.01-mA steps until the subject indicated that he/she felt the pulse again in two consecutive trials. This intensity was defined as the PT. During all experiments, stimulation intensity was set to 3 times the PT. If the subject reported this to be painful, the intensity was reduced to below pain threshold.

Timing of electrical stimulation

In order to elicit SAI, electrical stimulation was applied at specific intervals before each TMS pulse. The TMS timings described hereafter are reported relative to the first of the three pulses in the somatosensory stimulation train. For each experiment, a control condition was included wherein the sensory stimulation was presented 70 ms *after* the TMS pulse, a timepoint where it could not influence the MEP that had already occurred. These control trials (10 per block) were randomly intermixed with all other trials containing pre-TMS sensory stimulation, and were used for comparison of MEP amplitudes against pre-stimulated trials.

Experiment 1

There were two experimental sessions on two separate days. On one day TMS was applied on the dominant (left) hemisphere (MEPs in right FDI). On another day, TMS was applied on the non-dominant (right) hemisphere (MEPs in left FDI). This was to establish whether SAI differs depending on whether the dominant or non-dominant side is stimulated. Otherwise identical procedures (described below) were carried out on each day.

Although TMS was only applied to one hemisphere in each session, electrical stimulation was applied to both fingertips (right and left finger stimulation randomized). Along with demonstrating contralateral SAI (Fig. 1A, upper panel), this was to establish whether 'ipsilateral SAI' could be elicited, whereby the limb being electrically stimulated is on the same side as the hemisphere to which TMS is applied (Fig. 1A, lower panel).

As somatosensory information from the finger reaches the cortex ~23 ms following stimulation (the N20), we chose to apply TMS 30 ms after the onset of the finger stimulation train (N20 + 7), to coincide with the end of the electrical stimulation train reaching the cortex. This timepoint was expected to produce strong contralateral SAI but would be too early to elicit ipsilateral SAI, based upon earlier findings (Ragert et al., 2011; Conde et al., 2013). An additional TMS timepoint 45 ms following sensory stimulation (N20 + 22) was included, at which contralateral SAI should still be ongoing, and ipsilateral SAI may have commenced (Fig. 1A).

There were six different electrical stimulation conditions, each presented 10 times per block, in random order: (1) Stimulation applied to the right finger 30 ms before TMS, (2) stimulation applied to the right finger 45 ms before TMS, (3) stimulation applied to the right finger 70 ms after TMS (right control), (4) stimulation applied to the left finger 30 ms before TMS,

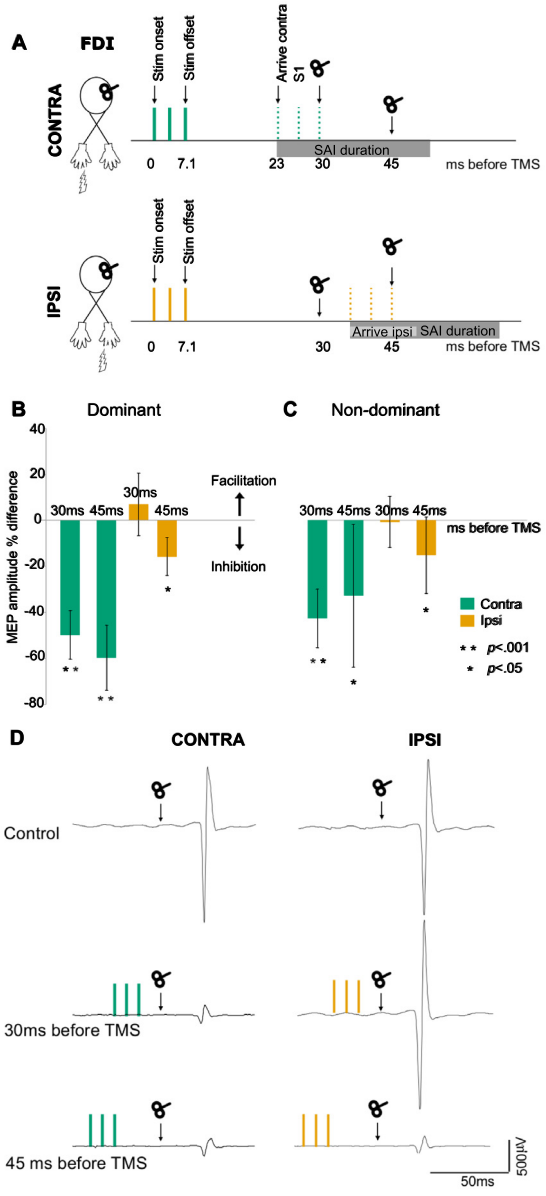

Fig. 1. Contralateral and Ipsilateral SAI for dominant and non-dominant First Dorsal Interosseus (FDI). Panel A depicts the experimental protocol. TMS was applied at 30 ms and 45 ms following sensory stimulation (Stim). Control MEPs were also collected, where sensory stimulation was applied 70 ms *after* TMS (not shown): Sensory stimulation of the finger contralateral to TMS is shown in the upper panel, with the arrival of contralateral input to S1 marked at 23 ms; Sensory stimulation of the finger ipsilateral to TMS is shown in A (lower panel), with the estimated window for the arrival of somatosensory information to the ipsilateral hemisphere from ~38 to 48 ms following stimulation (marked by a light grey rectangle). Panel B&C show the change in MEP amplitude relative to control MEPs (percentage difference, Y-axis) when sensory stimulation is applied at either the ipsilateral or contralateral limb at different timepoints prior to TMS (X-axis). Values below 0 indicate that electrical/sensory stimulation prior to TMS inhibited the motor response (SAI). Separate sessions were conducted for the dominant (B) and non-dominant (C) limbs. Error bars represent 95% confidence intervals. Panel D shows EMG traces from the dominant limb FDI of one representative subject. Single MEPs are shown from trials with ipsilateral and contralateral stimulation 30 ms and 45 ms prior to TMS. Control MEPs with no prior electrical stimulation are also shown (upper panels). In these trials, finger stimulation occurred 70 ms after TMS.

(5) stimulation applied to the left finger 45 ms before TMS, (6) stimulation applied to the left finger 70 ms after TMS (left control).

This block (total of 60 TMS pulses) was repeated twice (to collect 20 MEPs per condition), with a break of 5 min in between during which the PT was re-tested for both fingers.

Experiment 2

TMS was applied on or close to the vertex, at a location that produced equal sized bilateral MEPs in both TA muscles, with the coil at a 0° angle to evoke posterior–anterior current flow deep in the interhemispheric fissure. Only the right foot was electrically stimulated, allowing measurement of both the 'contralateral' and 'ipsilateral' effects simultaneously. MEPs recorded in the right TA were considered to reflect the hemisphere 'contralateral' to somatosensory stimulation and those in the left TA reflected the hemisphere 'ipsilateral'. Somatosensory stimulation was applied at 3 different timepoints before TMS: 45 ms, 50 ms and 55 ms. As somatosensory information from the foot takes ~40 ms to travel to the cortex (N40), these timepoints can be considered as N40 + 5, N40 + 10 and N40 + 15 ms. Contralateral SAI is expected at all three timepoints, and ipsilateral SAI may only emerge at N40 + 15 and beyond (Fig. 2A).

Experiment 3

Both upper (FDI) and lower limb (TA) were tested in two separate sessions. The purpose of this experiment was to determine the timing of the onset of ipsilateral SAI. Hence, only the right limb (finger or foot) was electrically stimulated. MEPs were recorded from left FDI or TA to reflect inhibitory processes in the right (ipsilateral) hemisphere. Identical stimulation timepoints (relative to contralateral N20/N40) were tested for both FDI and TA; N20/N40 + 15, + 18, + 20, + 22, + 24, + 40 (Fig. 3A). Hence, some of the timepoints provide a replication for those tested in Experiments 1 & 2. Additionally, one extra timepoint at N20 + 26 was tested for FDI but not for TA.

Data analyses and processing

The rms of the background EMG recorded in FDI and TA was calculated for a window of 105–5 ms before TMS onset. If the value was greater than 10 μV, the corresponding MEP was disregarded. Additionally, for each subject, the mean and standard deviation of the background EMG scores were computed and trials with rms EMG larger than the mean plus 2.5 SDs were removed from the analysis. Trials with exceptionally large MEP amplitudes were also excluded, i.e., when the peak-to-peak amplitude exceeded Q3 + 1.5 times the interquartile range (i.e. the box plot criterion for outliers). For the remaining MEPs, the mean (peak–peak) amplitude was calculated separately for each stimulation condition. According to these screening criteria, 79 ± 10.4% of the trials (Exp. 1) were retained for further analyses (Exp. 2: 84 ± 5.3%, Exp. 3: 83 ± 5.9%).

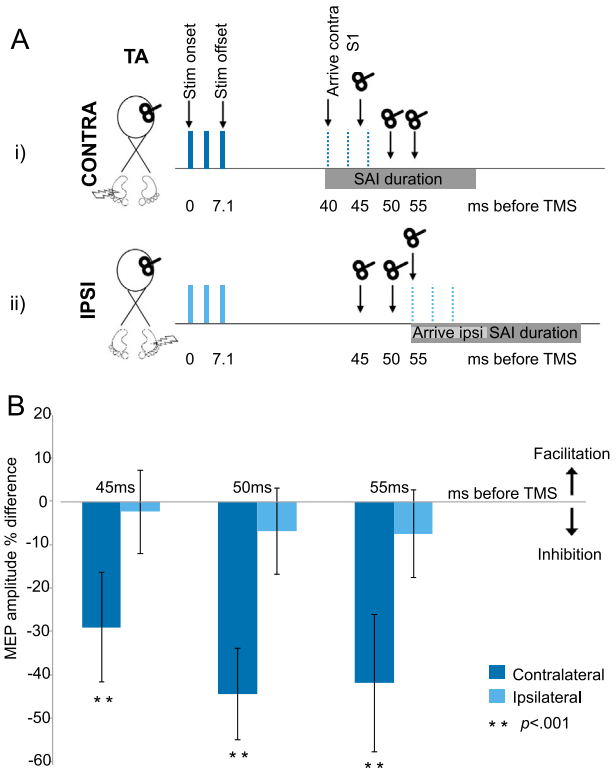

Fig. 2. Contralateral and Ipsilateral SAI for the lower limb (Tibialis Anterior, TA). Panel A depicts the experimental protocol. TMS was applied at 45 ms, 50 ms and 55 ms following sensory stimulation (Stim). Control MEPs were also collected, where stimulation was applied 70 ms *after* TMS (not shown). For ease of interpretation the diagrams show TMS applied laterally to one hemisphere (in reality, the coil was placed over the vertex in order to elicit bilateral MEPs): (i) Sensory stimulation of the contralateral foot, with the arrival of sensory information to contralateral S1 marked at 40 ms; (ii) Sensory stimulation of the ipsilateral foot. Light grey rectangle indicates a possible time window for arrival of sensory information to the ipsilateral hemisphere ranging from 55 to 65 ms. Panel B shows the percentage difference in MEP amplitude relative to control MEPs (Y-axis). Values below 0 indicate that electrical stimulation prior to TMS inhibited the motor response. Error bars represent 95% confidence intervals.

Statistical analyses

The dependent variable was peak-peak MEP amplitude. Data were checked for normality using a Shapiro–Wilk test. In cases where raw variables deviated from normality, a log transformation was applied prior to further statistical procedures. Planned comparisons conducted following repeated measures ANOVA models were used to establish if MEP amplitudes were different from control MEPs when TMS was preceded with sensory stimulation at different timings. The assumption of sphericity was tested, and where violated, the Greenhouse–Geisser correction applied. ANOVA factors were 'hand dominance' (MEPs collected from the dominant or non-dominant limb, Exp. 1 only), 'timing' (sensory stimulation prior to TMS) and 'stimulation side' (contralateral or ipsilateral to TMS). Additionally in Experiment 3, 'limb' (leg or finger) was also included as part of a 2-way limb × timing model. Partial Eta Squared (η_p^2) effect sizes are reported to aid with interpretation,

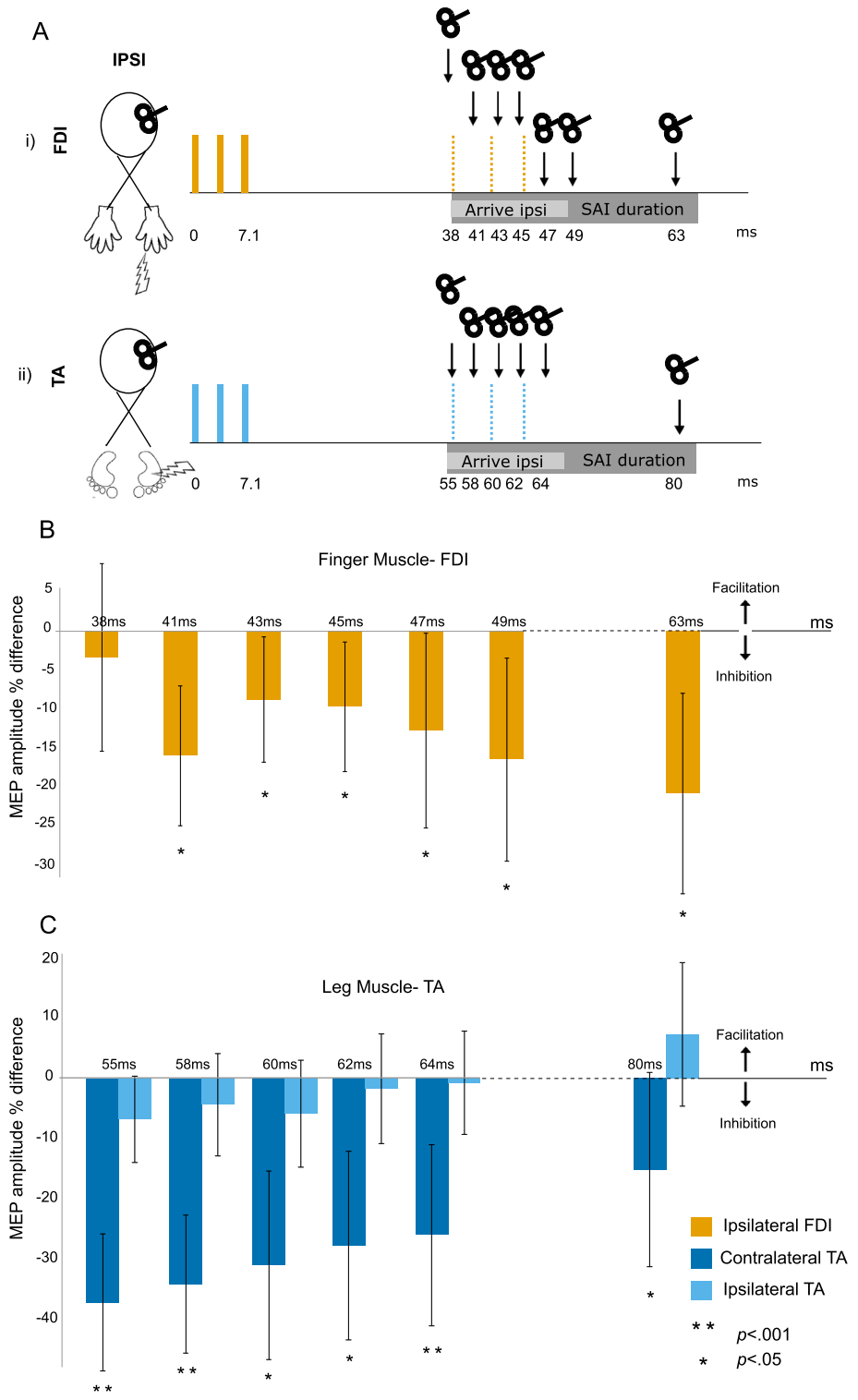

Fig. 3. Onset of Ipsilateral SAI. Panel A depicts the experimental protocol. TMS was applied at various timepoints following electrical stimulation of (i) the fingertip, or (ii) the dorsal surface of the foot. The light grey rectangle indicates a possible time window for arrival of sensory information to the ipsilateral hemisphere. Sensory stimulation timepoints are comparable for first dorsal interosseous (FDI) and Tibialis Anterior (TA) relative to the contralateral N20 (e.g. 38 ms is N20 + 15 for FDI and 55 ms is the equivalent timepoint for TA). An additional timepoint at 49 ms (N20 + 26 ms) is shown for FDI. Due to the opportunity to collect MEPs bilaterally during lower limb TMS, contralateral SAI for TA at the same timepoints is also shown/presented. Control MEPs were collected, where stimulation was applied 70 ms *after* TMS (not shown). Panel B represents/shows/depicts/presents the percentage difference in MEP amplitude relative to control MEPs (Y-axis). Values below 0 indicate that electrical stimulation prior to TMS inhibited the motor response. Error bars represent 95% confidence intervals.

where 0.01 indicates a 'weak' effect, 0.09 is 'moderate' and 0.25 is large. The number of planned pairwise comparisons was specified in advance and restricted to not exceed the threshold quantity requiring alpha level adjustment, in accordance with the modified Bonferroni procedure (Keppel and Wickens, 1991). The alpha level was fixed at 0.05. All statistical analyses were conducted using SPSS (Version 22.0, Armonk, NY, IBM Corp.)

RESULTS

Experiment 1

Here we tested whether ipsilateral SAI could be detected when electrical stimulation was applied 30 ms (N20 + 7 ms) and 45 ms (N20 + 22 ms) before TMS, i.e. one timing too early to allow for transcallosal information transfer (30 ms) and one where transfer should have already occurred (45 ms). We first tested whether SAI (ipsi and contra) differed for the dominant and non-dominant limb (FDI), in order to ensure that any 'ipsilateral' effects reported hereafter were not influenced simply by the fact that the non-dominant limb was the target. A non-significant '*hand dominance*' × '*stimulation side*' × '*timing*' interaction ($p = .92$) verified that there was no significant influence of hand dominance on the observed effects, therefore subsequent statistical models were executed independently for the dominant and non-dominant limbs.

For the dominant limb (Fig. 1B) there was a significant '*stimulation side*' × '*timing*' interaction ($F(2,44) = 18.63$, $p < .001$, $\eta_p^2 = .46$). Pairwise comparisons revealed that strong SAI was observed when electrical stimulation of the contralateral FDI occurred 30 ms ($p < .001$) and 45 ms ($p < .001$) prior to TMS. When the electrical stimulation was ipsilateral, no SAI was observed at the earlier timepoint (30 ms), but had emerged by 45 ms ($p < .05$, Fig. 1B, D). An identical pattern of results was obtained for the non-dominant limb (Fig. 1C), i.e. a significant '*stimulation side*' × '*timing*' interaction ($F(1.48,25.11) = 4.21$, $p < .05$, $\eta_p^2 = .60$), with contralateral SAI evident at 30 ms ($p < .001$) and 45 ms ($p < .05$), but ipsilateral SAI only at 45 ms ($p < .05$, Fig. 1B).

Experiment 2

Next we tested whether contralateral and ipsilateral SAI is present in the lower limb TA when the dorsal surface of the foot was electrically stimulated (Fig. 2A). Repeated measures ANOVA indicated that there was a significant '*stimulation side*' × '*timing*' interaction ($F(1.85,25.90) = 8.12$, $p < .05$, $\eta_p^2 = .37$). Pairwise comparisons revealed significant SAI for the contralateral TA at all 3 timepoints (45 ms, 50 ms, 55 ms; all $p < .001$) but surprisingly, not at any of the timepoints for the ipsilateral TA (all $p > .07$; Fig. 2B). This was not due to floor effects, as the amplitudes of the ipsilateral TA control MEPs were sufficient (*Mean* 310 μV) and comparable to those for the contralateral TA (*Mean* 350 μV).

Experiment 3

Finally we aimed to determine the timepoint at which ipsilateral SAI first emerges. Based on the lack of ipsilateral SAI for TA (Exp. 2), several later timepoints were chosen to probe whether ipsilateral SAI for leg may simply occur later than the timepoints already tested (Fig. 3A). Comparable electrical stimulation timepoints were tested for FDI and TA, all taken relative to the contralateral N20/N40 (e.g. N20 + 15 ms is equivalent to electrical stimulation 38 ms prior to TMS for FDI and 55 ms prior to TMS for TA). An additional timepoint at 49 ms (N20 + 26 ms) was tested for FDI. Due to the opportunity to collect bilateral MEPs during lower limb TMS, contralateral SAI for TA is also reported. A repeated measures ANOVA with factors '*limb*' (leg and finger)' and '*timing*' indicated a significant '*limb*' × '*timing*' interaction ($F(3.24,61.49) = 4.16$, $p < .05$, $\eta_p^2 = .18$). Pairwise comparisons revealed that ipsilateral SAI for the FDI was not present at 38 ms, but was significant at all timepoints from 41 ms onward (41, 43, 45, 47, 49, 63 ms, all $p < .05$, Fig. 3B, C). For TA, pairwise comparisons revealed no ipsilateral SAI at any timepoint (all $p > .2$). A separate ANOVA was conducted for the TA alone, combining ipsilateral and contralateral MEPs at each timepoint (Fig. 3C). There was a significant '*stimulation side*' × '*timing*' interaction ($F(3.65,69.34) = 4.90$, $p < .05$, $\eta_p^2 = .20$). Pairwise comparisons revealed significant SAI at all timepoints for the contralateral TA (all $p < .05$), but not at any timepoint for ipsilateral TA (all $p > .2$). Again, the amplitudes of ipsilateral TA MEPs were sufficient to rule out floor effects (*Mean* 310 μV) and comparable to those for the contralateral TA (*Mean* 290 μV).

DISCUSSION

We used a SAI paradigm at rest to investigate whether somatosensory information modulates M1 activity in the hemisphere *ipsilateral* to the stimulated limb. The most notable finding is that ipsilateral SAI was robustly demonstrated for the upper limb (Exp. 1 & Exp. 3) but not for the lower limb (Exp. 2 & Exp. 3), and that the earliest ipsilateral upper limb SAI only occurs when the delay between stimulating the limb and probing M1 was larger than 41 ms, corresponding to the N20 + 18 ms.

Contralateral SAI in hand and foot

Consistent with previous reports (Maertens de Noordhout et al., 1992; Tokimura et al., 2000; Helmich et al., 2005; Bikmullina et al., 2009; Cash et al., 2015), we found strong contralateral SAI for the upper limb. While Helmich et al. (2005) found that SAI was more pronounced in hand muscles of the dominant upper limb, in our protocol we did not observe a significant influence of handedness, and revealed large effect sizes regardless of whether we tested the dominant or non-dominant limb. Contralateral SAI for the hand first occurs at a time corresponding to the somatosensory N20 + 1 ms (Tokimura et al., 2000), i.e. immediately when the sensory signal from the limb reaches the cortex. As H-reflexes and

direct stimulation of corticospinal axons are unaffected during upper limb SAI (Delwaide and Olivier, 1990; Tokimura et al., 2000), it is generally accepted that the inhibition is cortically generated. While SAI has been repeatedly demonstrated for the upper limb, literature concerning lower limb SAI is much more heterogeneous. Reports have found contralateral inhibition in the lower limb following tibial nerve stimulation at time points earlier than the somatosensory N40 (Roy et al., 2008), or none at all (Bikmullina et al., 2009). Our paradigm (using a train of 7.1 ms and evoking MEPs in TA after stimulating the skin on the dorsal surface of the foot) revealed robust and reproducible contralateral lower limb SAI at timepoints ranging from at least 45 ms (Exp. 2) to 80 ms following stimulation (Exp. 3) (all effect sizes > 0.2). Indeed, Roy et al. (2008) and Bikmullina et al. (2009) actually report facilitation of TA within this interval, which they demonstrate to be cortically generated. Such contrasting findings may be explained by the fact that different nerves were targeted and different types of stimulation used in each of the aforementioned protocols. While the cutaneous afferent signals in our study most likely reach the cortex via the peroneal nerve, direct stimulation of the tibial nerve (such as in Roy et al.) or stimulation of the great toe (Medial plantar nerve – such as in Bikumullina et al.) are likely to exert heterogeneous effects on the cortex, as it has been shown that different lower limb nerves generate cortical potentials with different somatosensory-evoked potential (SEP) positive and negative peak latencies and scalp topographies (Vogel et al., 1986; Yamada et al., 1996; Hauck et al., 2006). In fact, as the tibial nerve and the medial plantar nerve both carry cutaneous afferent signals from the bottom (plantar) surface of the foot, whereas we targeted the top (dorsal) surface, it is possible that this may account for the change in polarity of our results; stimulation of somatosensory afferents from the plantar surface may primarily facilitate TA upon arrival to the cortex, whereas afferents traveling from the dorsal surface inhibit TA. Although we can only speculate, this may be a reflection of the functional purpose of SAI, as the demands for sensorimotor integration regarding TA are different for the types of information traveling from the plantar and dorsal surfaces of the foot, and likewise for lower vs. upper limbs.

Ipsilateral SAI for upper but not lower limb

Only for the upper limb, we elicited ipsilateral SAI at all stimulation timepoints that were at least 18 ms following the arrival of the sensory signal to the contralateral S1. This is similar to the timing reported in a previous study with a small sample (n = 6), whereby digital stimulation of the index finger caused maximal MEP suppression in the ipsilateral hemisphere 15 ms later than the onset of contralateral suppression (Manganotti et al., 1997). Additionally, it should be noted that the magnitude of ipsilateral SAI was noticeably lower than that of contralateral SAI, while the overall magnitude of ipsilateral SAI did not differ depending on whether the tested hemisphere was ipsilateral to the dominant or the non-dominant hand.

The notion that contralateral SAI is a direct readout of the fundamental process whereby sensory input affects motor output is generally accepted (Tokimura et al., 2000). As such, ipsilateral SAI may serve as a valuable indicator of the process of *bilateral* sensorimotor integration, whereby sensory information from one limb is processed concurrently in the ipsilateral hemisphere to allow direct modulation of the motor cortical output from *both* limbs. This type of information sharing between hemispheres is essential for the upper limbs to achieve tasks that require complex bimanual (symmetrical or asymmetrical) cooperation, such as buttoning a shirt. Such a demand for fine sensory-guided motor control is not, however, characteristic of the lower limbs and may explain the absence of lower limb ipsilateral SAI in the current experiments. If ipsilateral SAI reflects the process of integrating unilateral sensory information with bilateral motor output, there may be no functional requirement for such a mechanism in the lower limb. Anatomically, this is also reflected in the fact that the proportion of neurons in the foot region of S1 that responds to ipsilateral stimulation is notably smaller than those in the hand region (Iwamura, 2000).

Potential neural pathways mediating ipsilateral SAI in upper limb

The onset timing of ipsilateral SAI in the finger starting 41 ms after sensory stimulation allows some assumptions to be made regarding the neural pathways that may be involved. Contralateral SAI emerges immediately following arrival of the sensory input to the cortex. However, whether SAI occurs due to the direct arrival of the sensory signal to M1, or via S1–M1 connections, is unknown (Fig. 4A). We propose that ipsilateral SAI occurs upon the arrival of the same sensory input to the ipsilateral cortex, though delayed by a fixed timing reflecting the conduction time within the brain. Ipsilateral SAI emerged from 41 ms onward, suggesting that by this time, the sensory information has traveled from the contralateral to the ipsilateral hemisphere, and the process of sensorimotor integration within M1 has occurred.

Our data suggest that the phenomenon of ipsilateral SAI occurs immediately following arrival of the sensory signal to the ipsilateral hemisphere, pointing to some candidate pathways that represent the earliest, fastest transmission route for ipsilateral sensory input to influence motor output. As it is known that ipsilateral S1 responses cannot occur without passing via contralateral S1 (Iwamura et al., 1994), we suggest a transcallosal route for this phenomenon. Whether ipsilateral SAI occurs via S1–S1 (Fig. 4B iii) or M1–M1 connections (Fig. 4B i, ii) is impossible to say based on the current investigation alone. One suggestion is that intrahemispheric S1–M1 communication occurs in the receiving hemisphere prior to M1–M1 crossing, whereby somatosensory input arrives at S1 (from the fingertip) after 23 ms, and takes approximately 5 ms to travel to M1 in the same hemisphere (Goldring et al., 1970). Subsequently it could take anywhere between 6 and 50 ms to exert an inhibitory influence on the opposite M1 (Reis et al., 2008). Therefore, signals may arrive at the ipsilateral M1 anywhere between 34 and 78 ms following stimulation. As we observed ipsilateral SAI from 41 ms

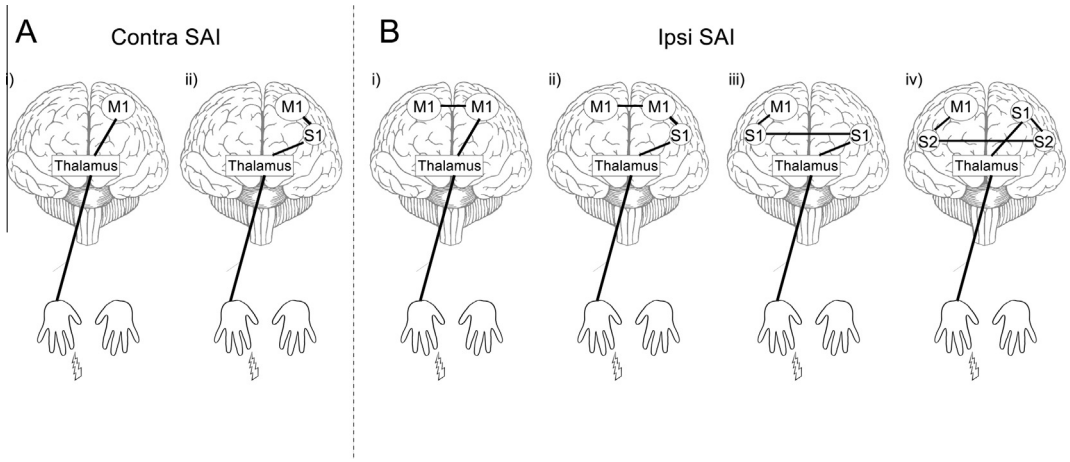

Fig. 4. Neural pathways for contralateral and ipsilateral SAI. Panel A depicts two potential pathways for contralateral somatosensory afferent information to influence M1, i.e. (i) a direct thalamic connection to contralateral M1 or (ii) signals first arriving at contralateral S1 and being transmitted subsequently to M1. Panel B depicts four possible neural pathways for ipsilateral SAI to occur: (i) direct transcallosal transfer between homologous M1; (ii) intrahemispheric S1–M1 communication in the receiving hemisphere prior to M1–M1 crossing. (iii) Direct S1–S1 transcallosal transmission, whereby sensory signals arrive at contralateral S1 after ~23 ms, and take ~13–20 ms to cross the corpus callosum (Allison et al., 1989; Karhu and Tesche, 1999). With an additional 5 ms for intrahemispheric S1–M1 communication (Goldring et al., 1970), the information may influence the contralateral M1 at the earliest 38–48 ms following stimulation, which encompasses the 41-ms onset of ipsilateral SAI found in the current study; (iv) signal transmission via S2.

onward, the current data cannot rule out this possibility. However, as it is known that some regions of S1 possess dense homologous anatomical connectivity (Killackey et al., 1983; Iwamura, 2000; Iwamura et al., 2001), while the posterior region of M1, which primarily receives somatosensory input (Stepniewska et al., 1993) is known to be poorly connected (Rouiller et al., 1994), it could be suggested that S1–S1 transfer is the most likely candidate. By this route, somatosensory signals arrive at contralateral S1 after ~23 ms, and take ~13–20 ms to cross the corpus callosum (Allison et al., 1989; Karhu and Tesche, 1999). With an additional 5 ms for intrahemispheric S1–M1 communication (Goldring et al., 1970), the information may influence the contralateral M1 at the earliest 38–48 ms following stimulation, which encompasses the 41-ms onset of ipsilateral SAI found in the current study (Fig. 4B iii). Of course, higher-level sensorimotor information transfer and processing will also occur after longer latencies, mediated by different pathways involving e.g. Secondary Sensory Cortex (S2) (Fig. 4B iv). S2 contralateral scalp potentials are first detected with a delay of ~40 ms following stimulation of the wrist (Hari et al., 1983, 1984, 1990, 1993; Forss and Jousmäki, 1998; Frot and Mauguière, 1999). Allowing for an additional S2–S2 transcallosal conduction time of ~15 ms (Hari et al., 1993; Hoechstetter et al., 2000; Wegner et al., 2000), the earliest ipsilateral potentials are detected from 50 ms onward (Karhu and Tesche, 1999). Hence it is more likely that the transcallosal transfer of the afferent signal occurs at an earlier stage of processing, as we report ipsi SAI much earlier than this pathway would allow.

While the evidence from the present TMS-based electrophysiological recordings appear to point toward a cortical locus for ipsilateral SAI since the onset timing coincides with the potential transmission time of the stimulus to the ipsilateral hemisphere, we must acknowledge that using this methodology we cannot provide conclusive confirmatory evidence that the inhibition has not been generated spinally. It is tempting to suggest that while studies have demonstrated that contralateral SAI is cortically generated, the same should be the case for ipsilateral SAI, but without using direct epidural spinal recordings, we cannot yet rule out the possibility that spinal inhibition plays a role in this phenomenon.

Potential clinical applications of contralateral and ipsilateral SAI

Conventionally, contralateral SAI is often used as a test for the function of cholinergic inhibition in the cortex and is significantly reduced in Alzheimer's disease (Di Lazzaro et al., 2004). Additionally, it is reduced in stroke survivors, and the level of SAI in the affected hemisphere correlates with functional recovery outcomes (Di Lazzaro et al., 2012). As both contralateral and ipsilateral SAI provide a valuable and time-specific reflection of the earliest transmission of sensory information within and between hemispheres, it is also possible that this may serve as a useful non-invasive tool to measure reorganization of sensorimotor pathways in disorders such as Cerebral Palsy or X-linked Kallman's syndrome. In some instances of Cerebral Palsy, the early unilateral brain lesion can lead to ipsilateral corticospinal tract reorganization where motor control of both upper limbs is confined to the non-lesioned hemisphere. As such, there are different 'types' of motor organization: contralateral, ipsilateral, and mixed (i.e. the paretic upper limb is controlled by both hemispheres) (Guzzetta et al., 2007; Staudt, 2010). Interestingly, somatosensory processing typically remains contralateral, even in cases of ipsilateral corticospinal tract reorganization (Guzzetta et al., 2007). The type of motor reorganization has a direct impact on the capacity for functional gains following upper limb rehabilitation in these children (Gordon et al., 2013). As such, the development of a new biomarker using SAI to identify

abnormalities in sensory-motor transmission would be a massive advance for the field.

Limitations and future directions

In the current investigation, a triplet of 3 pulses of electrical stimulation was applied to the fingertip or foot, which differs from the traditional application of one single pulse. Our data show that this evokes contralateral SAI within the normally reported timeframes (i.e. corresponding to the transmission time of sensory stimuli to cortex) suggesting that the earliest responses were evoked by the first of the three stimulations. However, we acknowledge that the current study does not address the impact that this may have upon the duration and offset of contralateral or ipsilateral SAI. Even with interstimulus intervals up to 63 ms for finger and 80 ms for foot, the inhibition generated by the ipsilateral somatosensory stimulation persisted, which is longer than the reported durations of contralateral SAI. Currently, we do not know whether this extended duration is due to the fact that this is *ipsilateral* SAI, which may simply be longer in duration than standard contralateral SAI, or whether this may be due to the inclusion of the longer duration of stimulation that is provided by the triplet. While the detection of the offset of SAI (and the underlying mechanisms) was not a priority in the present study, this may be of interest for future investigations of the basic physiology and characteristics of ipsilateral SAI.

It is important to note that the first statistically significant ipsilateral SAI detected in the upper limb at 41 ms after sensory stimulation is based on group data ($n = 20$). Variations in height and path lengths between individuals inevitably lead to differences in the timing of the N20, which was not quantified in this study. However, as the variability of the N20 is within the resolution of ± 1 ms between people for the upper limb (Suzuki and Mayanagi, 1984), the estimates reported herein are likely to be sufficiently accurate. However, as leg lengths exhibit more variability between individuals, the relative timing of the arrival of stimulation to the cortex may be also be more variable. As SAI was present following contralateral stimulation of the foot even at the earliest tested timepoints, we cannot draw any conclusions regarding the onset time of contralateral SAI in the TA muscle following stimulation on the top of the foot (a combination which has not previously been tested), which may be of interest for future investigations. Importantly, even when contralateral SAI was present at all the tested timepoints, no ipsilateral SAI was detected at any. The variations in height and path lengths are more likely to be relevant in influencing arrival of the stimulus to the contralateral hemisphere, and not have such an impact upon the subsequent transfer of the signal across the corpus callosum. Hence, while variability in leg lengths may have impacted upon the detection of the onset time of contralateral SAI, it is not likely that this factor was the sole determinant of the lack of ipsilateral SAI reported herein.

Additionally, while the timing of the onset of ipsilateral SAI which coincided with the predicted time of arrival of the somatosensory signal to the ipsilateral cortex (following transcallosal transfer) has led to our suggestion that the inhibition is generated cortically, a future investigation using epidural spinal recordings would clarify potential cortical contributions.

CONCLUDING REMARKS

Data from this series of experiments support the existence of a highly reproducible ipsilateral SAI process analogous to the widely reported contralateral SAI for the upper limb. As the onset of ipsilateral inhibition is delayed ~18 ms relative to the contralateral effect, we suggest that transcallosal transfer mediates this interhemispheric sensorimotor communication at an early stage of processing involving bilateral S1. Additionally, we reveal the novel finding of a complete absence of ipsilateral SAI in the lower leg, perhaps reflecting the lack of requirement for complex bilateral sensorimotor integration for the feet, in contrast to the hands. As SAI can be used to assess the function of sensorimotor circuitry in disease states, *ipsilateral* SAI may serve as a useful readout of the process of sensorimotor integration *between* hemispheres.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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