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Somatosensory-motor cortex interactions measured using dual-site transcranial magnetic stimulation

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ABSTRACT

Background: Dual-site transcranial magnetic stimulation (ds-TMS) is a neurophysiological technique to measure functional connectivity between cortical areas.
Objective/Hypothesis: To date, no study has used ds-TMS to investigate short intra-hemispheric interactions between the somatosensory areas and primary motor cortex (M1).
Methods: We examined somatosensory-M1 interactions in the left hemisphere in six experiments using ds-TMS. In *Experiment 1* (n = 16), the effects of different conditioning stimulus (CS) intensities on somatosensory-M1 interactions were measured with 1 and 2.5 ms inter-stimulus intervals (ISIs). In *Experiment 2* (n = 16), the time-course of somatosensoy-M1 interactions was studied using supra-threshold CS intensity at 6 different ISIs. In *Experiment 3* (n = 16), the time-course of short-interval cortical inhibition (SICI) and effects of different CS intensities on SICI were measured similar to Experiments 1 and 2. *Experiment 4* (n = 13) examined the effects of active contraction on SICI and somatosensory-M1 inhibition. *Experiments 5* and *6* (n = 10) examined the interactions between SAI with either 1 ms SICI or somatosensory-M1 inhibition.
Results: *Experiments 1 and 2* revealed reduced MEP amplitudes when applying somatosensory CS 1 ms prior to M1 TS with 140 and 160% CS intensities. *Experiment 3* demonstrated that SICI at 1 and 2.5 ms did not correlate with somatosensory-M1 inhibition. *Experiment 4* found that SICI but not somatosensory-M1 inhibition was abolished with active contraction. The results of *Experiments 5–6* showed SAI was disinhibited in presence of somatosensory-M1 while SAI was increased in presence of SICI.
Conclusion: Collectively, the results support the notion that the somatosensory areas inhibit the ipsilateral M1 at very short latencies.

Introduction

Somatosensory input from peripheral tactile, joint, tendon and muscle receptors provide sensory information to the central nervous system that is used to control movements. Specifically, proprioceptive input can provide information about limb position, movement sense, muscle tension and force that can be used to prepare, execute and correct on-going movements [1,2]. Sensorimotor integration is known to be impaired in a variety of neurological disorders including Parkinson's disease [3], dystonia [3], Alzheimer's disease [4], autism spectrum disorders [5] and stroke [6]. Therefore, defining somatosensory and motor interactions is necessary for understanding the neurophysiological mechanisms required for motor control and how their disruption leads to motor impairments.

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Dual-site transcranial magnetic stimulation TMS (ds-TMS) is a method that investigates cortico-cortical interactions between multiple cortical areas [7,8]. The ds-TMS technique measures the effects of a TMS conditioning stimulus (CS), applied over either intra- or inter-hemispheric locations, on corticospinal excitability measured by the amplitude of motor-evoked potentials (MEPs) evoked by TMS over the primary motor cortex (M1). The results with a prior CS are compared to those with test stimulus (TS) alone. To date, no study has used ds-TMS to measure the functional connectivity between ipsilateral primary somatosensory cortex (S1) and M1.

Previous studies using ds-TMS have investigated cortical connections by stimulating several intra-hemispheric cortical areas known to interact with M1 including the dorsal premotor cortex (PMd) [9–14], ventral premotor area (PMv) [7,9,12,15,16], supplementary motor area (SMA) [9,17], pre-SMA [7,18], dorsolateral prefrontal cortex (DLPFC) [19], and posterior parietal cortex (PPC) [20–28]. Inhibition (reduced MEP amplitudes) and facilitation (increased MEP amplitudes) have been demonstrated dependent on location, CS intensity, inter-stimulus intervals (ISIs), and whether participants were at rest or contracting the target muscle (see Ref. [29] for review).

Although short intra-hemispheric somatosensory-motor interactions have not been tested, previous research has investigated inter-hemispheric somatosensory-M1 interactions, demonstrating inhibition at 30, 40 and 50 ms ISIs with CS intensities above 1.4 active motor threshold (AMT) [30,31]. Furthermore, applying CS to ipsilateral area 5, an area just posterior to S1 involved in somatosensory-motor control, was shown to facilitate M1 at 6 ms ISI while inhibiting M1 at 40 ms ISI during vibration of digits but not at rest using CS intensity of 90% resting motor threshold (RMT) [28]. Shorter ISIs were not investigated. It has been well-documented that stimulation of the median nerve (MN) or digital nerves followed by TMS over the contralateral M1 can induce decreases or increases in the MEP amplitude at short or long intervals [32–40]. Short-latency afferent inhibition (SAI) can begin as early at 19 ms ISI following MN stimulation with maximal inhibition at an ISI of ~21 ms [37]. It is unclear if SAI relies on direct S1 to M1 connections since studies measuring N20 somatosensory-evoked potentials (SEPs) or M20 somatosensory-evoked fields (SEFs) have shown that activity in primary somatosensory cortex (S1) begins between 19 and 21 ms, whereas subcortical areas such as the thalamus show peak activity earlier between 16 and 18 ms after MN stimulation [41–47]. Since SAI can be shown as early as 19 ms, it is plausible that thalamo-cortical connections are responsible for this inhibitory circuit. However, it is unclear if cortico-cortical interactions between ipsilateral S1 and M1 can occur at short-intervals between 1 and 6 ms and as early as 1 ms consistent with the optimal timing of SAI.

We hypothesized that stimulation of the ipsilateral somatosensory areas would reduce M1 excitability at an ISI of ~1–6 ms. This is consistent with the notion that ipsilateral somatosensory-M1 interactions drive the inhibition from SAI at 21 ms. We also hypothesized that as CS intensity increased, the amount of somatosensory-M1 inhibition increase based on previous results in SAI [39]. For our control experiments, we hypothesized that SICI [51,52] but not somatosensory-M1 interactions would decrease with target muscle contractions. Additionally, it was hypothesized that SAI would be disinhibited in presence of SICI [53] but not somatosensory-M1 interactions. It is important to note that measuring somatosensory and M1 interactions is technically challenging with ds-TMS due to the close proximity between these locations. In fact, this would be impossible with most TMS coils, and therefore requires specialized, small TMS coils to measure. The goals of the current experiments were to examine whether ds-TMS could be used to investigate intra-hemispheric cortico-cortical somatosensory-M1 interactions and whether a fast inhibitory cortico-cortical circuit could be measured between 1 and 6 ms. We also examined whether there were dissociable effects of somatosensory-M1 inhibition and SICI with active contraction (compared to rest) and interactions with SAI.

Methods

Participants

Twenty-nine healthy right-handed volunteers (18 females, mean age 25.8 ± 4.7 SD years, range 19–38 years) participated in the experiments. Handedness was determined by self-report to an abbreviated Waterloo Handedness Questionnaire [54]. In *Experiment 1*, 16 volunteers, 8 of whom also participated in our pilot experiment (see *Supplemental Material*), were included in the analyses. Four participant collections were terminated early and were excluded from analyses due to the inability to consistently evoke 1 mV MEPs with the small TMS coils. The same 16 volunteers (10 females, mean age 28.2 ± 4.5 SD years, range 20–38 years) included in *Experiment 1* also participated in *Experiments 2* and *3*. *Experiment 4* was conducted in 13 volunteers (8 females, mean age 22.8 ± 3 SD years, range 19–30 years) who did not participate in Experiments 1 through 3. *Experiments 5 and 6* included 10 of the volunteers (6 females, mean age 22.2 ± 2.4 SD years, range 19–26 years) who participated in Experiment 4. All participants underwent a neurological examination by a neurologist and had no contraindications to TMS [55]. Participants provided written informed consent in accordance with the Declaration of Helsinki. The experimental protocols for Experiments 1–3 were approved by the University Health Network (Toronto) Research Ethics Board and were conducted at the Krembil Research Institute (Toronto) while Experiments 4–6 were approved by the ethics committee and were conducted at the University of Lübeck.

Surface electromyography (EMG) recordings

Surface EMG was recorded using a tendon-belly montage from both the target first dorsal interosseous (FDI) muscle and non-target abductor pollicis brevis (APB) muscle on both hands with disposable surface 9 mm Ag-AgCl electrodes. The EMG signal was amplified (x1000) (Intronix Technologies Corporation., Model 2024F, Bolton, Ontario, Canada or Digitimer Limited, model D360, Welwyn Garden City Hertfordshire, UK), filtered (bandpass filtered 20 Hz–2.5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronic Design, Cambridge, United Kingdom) and stored on a computer for off-line analysis.

Transcranial magnetic stimulation (TMS)

Ds-TMS was performed using two figure-of-eight branding iron coils (inner diameter:25 mm) connected to two Magstim 200^2 stimulators (Magstim Company, Whitland, United Kingdom). The optimal position for activating the right FDI in M1 was identified and marked with a frameless stereotaxic neuronavigation system (Brainsight, Rogue Research, Montreal, Quebec, Canada) and co-registered with individual anatomical magnetic resonance imaging (MRI) scans. The location of M1, corresponding to the 'hand knob', was also marked directly on the scalp. Our M1 anatomical targets (Talairach coordinates (TC) based on Talairach atlas; group mean ± SD; n = 29; x = -24.71 ± 4.33, y = −16.80 ± 4.64, z = 56.63 ± 5.57) corresponded well with our actual M1 functional stimulation locations (TC; group mean ± SD; n = 29; x = -26.02 ± 7.18, y = −17.95 ± 7.55, z = 56.94 ± 5.85) in *Experiments*

1–6. There was no significant differences in the x, y, or z coordinates between the M1 anatomical and M1 stimulation locations ($F(2,56) = 0.53$, $p = 0.59$). AMT for the right FDI was determined while participants maintained a ~20% maximum voluntary contraction (MVC) aided by constant visual and auditory feedback. AMT was defined as the minimum stimulus intensity required to produce 5 out of 10 MEPs of at least 200 μV during contraction. The group mean (±SD) AMT for the 25 mm coils was 53.68% (±8.40%) of maximum stimulatory output (MSO). All TMS procedures were performed in accordance with IFCN guidelines [56].

During ds-TMS, the TS was applied with one coil over the left M1 at an intensity to evoke ~1.25 mV MEPs in the right FDI muscle. The group mean (±SD) MSO to evoke ~1.25 mV MEPs was 84.81% (±12.31%). The TS intensity was checked and adjusted prior to each block. All mean MEPs in the TS alone conditions were within the 0.5–2.0 mV range. All ds-TMS experiments were conducted at rest except for *Experiment 4a.* The second coil targeted the left S1 anatomical location with neuronavigation according to individually determined anatomical landmarks based on the individual MRI, although the actual somatosensory stimulation areas varied (see below). S1 anatomical location was defined as an area in the posterior portion in the post-central gyrus bordering the post-central sulcus at the same approximate dorsoventral level as the 'hand knob' region in M1, an area known to be functionally active during hand movements [57]. This area likely corresponds to Brodmann area (BA) 2 sub-division of S1 [58]. Due to the close proximity of S1 to M1 anatomical locations and the coil sizes, the actual somatosensory stimulation sites were adjusted to the closest physical location possible with both TMS coils on the scalp at the beginning of the experiment and remained constant throughout experimental sessions. Individual targeted anatomical (TC; group mean ± SD; n = 29; x = -33.58 ± 4.02,y = −33.73 ± 6.09, z = 50.32 ± 4.67) and actual somatosensory stimulation locations (TC; group mean ± SD; n = 29; x = -29.50 ± 9.26, y = −42.87 ± 9.59, z = 51.32 ± 7.24) from *Experiments 1–5* are presented in Table 1. Both coils were held tangentially to the scalp at 45° to the mid-sagittal line to induce posterior-anterior directed currents in the underlying cortical tissue (see Fig. 1).

Short-interval cortical inhibition (SICI) was measured using a figure-of-eight branding iron coil (inner diameter: 40 mm or 50 mm) connected to two Magstim 200^2 stimulators (Magstim Company, Whitland, United Kingdom). It should be noted that technical limitations of the Magstim 200^2 stimulators did not allow double pulse TMS through the same coil (e.g. SICI) using the smaller 25 mm coils. The group mean (±SD) AMT for 40/50 mm coils was 42.5% (±6.61%) of MSO. Stimulation over left M1 was roughly the same location used for the ds-TMS experiments using TS intensities to evoke ~1.25 mV MEPs in the right FDI and adjusted throughout the experiment; when required small adjustments in TS location were made to ensure stimulation with the different coils was on the motor hot-spot. The TS intensity was checked and adjusted prior to each block. All MEPs in the TS alone conditions were within the

Table 1
Anatomically-targeted S1 locations and actual somatosensory stimulation locations represented as Talairach coordinates (TC) based on Talairach Atlas (*x,y,z)* in mm. Euclidean distances between somatosensory stimulation and S1 anatomical location, mean somatosensory stimulation location and individual somatosensory stimulation location, and normalized MEPs for somatosensory-M1 1 ms interactions are also presented.

Participant	S1 anatomical targets			S1 stimulation sites			Euclidean Distance between M1 and S1 stimulation locations	Euclidean Distance between S1 anatomical and S1 stimulation locations	Euclidean Distance between mean S1 stimulation locations and individuals S1 stimulation locations	S1-M1 normalized MEP amplitude at 1 ms ISI with 160% AMT (mean from *Experiments 1 and 2* or *Experiment 4*a*)*
	X	Y	Z	X	Y	Z				
1	−35.27	−24.18	47.28	−35.27	−23.94	47.45	22.67	0.29	20.17	35.96
2	−39.27	−35.24	48.31	−48.77	−54.24	63.08	43.27	25.87	25.27	21.30
3	−35.86	−32.04	49.82	−32.02	−40.47	53.99	39.64	10.16	4.39	17.24
4	−32.31	−32.83	52.54	−37.55	−43.58	47.37	31.91	13.03	8.99	80.09
5	−36.84	−30.68	45.14	−21.06	−48.43	50.29	35.77	24.30	10.16	30.90
6	−33.54	−39.77	44.45	−33.22	−28.49	46.38	20.36	11.45	15.65	121.30
7	−43.52	−25.92	42.21	−34.3	−44.23	42.71	47.16	20.51	9.95	30.96
8	−28.63	−35.84	50.91	−22.31	−45.02	54.75	30.55	11.79	8.25	90.67
9	−35.63	−41.23	47.38	−33.86	−62.55	40.92	39.38	22.35	22.68	70.03
10	−34.8	−36.79	49.69	−48.49	−27.99	35.88	36.47	21.34	28.64	117.79
11	−36.83	−24.79	52.84	−26.64	−56.1	52.42	36.52	32.93	13.58	41.27
12	−35.21	−24.38	45.76	−21.71	−55	41.86	33.65	33.69	17.24	68.90
13	−28.77	−32.54	46.05	−29.48	−46.63	39.72	33.59	15.46	12.19	44.77
14	−24.03	−38.39	48.88	−13.45	−40.66	51.11	21.94	11.05	16.21	29.85
15	−32.79	−28.18	49.49	−12.58	−49.02	50.84	26.88	29.06	18.01	53.16
16	−34.15	−41.14	58.03	−12.31	−58.03	63.88	30.52	28.22	26.14	76.62
17	−32.32	−35.17	49.47	−23.63	−45.81	51.81	27.35	13.94	6.58	43.25
18	−36.57	−28.1	52.68	−33.93	−38.12	55.04	28.99	10.63	7.49	92.94
19	−24.83	−40.19	60.71	−24.81	−40.31	57.21	20.73	3.50	7.96	71.58
20	−33.75	−40.75	55.31	−37.83	−34.99	53.77	16.30	5.00	11.73	62.98
21	−34.44	−38.17	49.45	−29.86	−40.61	52.71	16.61	6.13	2.68	153.44
22	−30.09	−42.1	45.84	−22.18	−40.22	50.03	17.95	9.15	7.89	73.90
23	−33.13	−28.77	47.56	−26.97	−34.02	52.72	21.81	9.60	9.31	100.07
24	−35.14	−38	46.98	−21.02	−48.43	55.46	15.26	19.50	10.95	59.46
25	−33.22	−36.75	53.4	−29.75	−30.16	62.14	17.79	11.48	16.70	81.35
26	−33.66	−44.34	55.80	−29.93	−53.27	59.71	26.84	10.44	13.37	113.51
27	−33.05	−32.16	62.18	−37.68	−42.06	62.67	20.82	10.94	14.02	80.65
28	−29.12	−37.84	51.59	−35.62	−38.57	46.95	23.83	8.02	8.66	20.64
29	−32.98	−22.59	51.19	−39.34	−32.37	45.31	23.64	13.06	15.59	86.10
Mean (±SD)	−33.58 (±4.01)	−33.73 (±6.09)	50.32 (±4.67)	−29.50 (±9.26)	−42.87 (±9.59)	51.32 (±7.24)	28.04 (±8.66)	15.27 (±8.80)	15.67 (±7.20)	58.17% (±32.64)

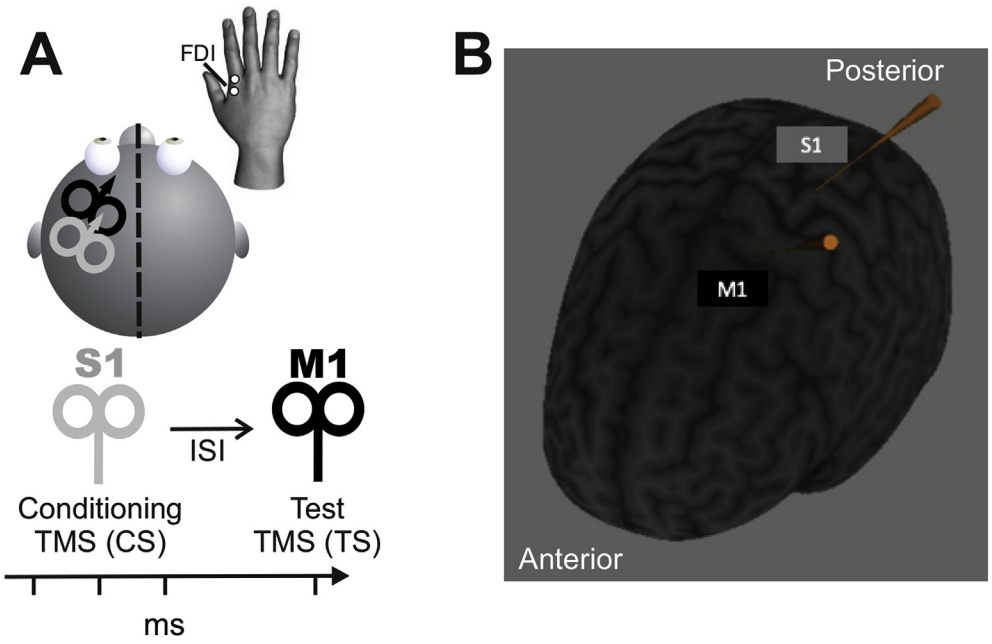

Fig. 1. Stimulation sites for somatosensory-M1 interactions.
A Schematic representation of the coil positions with posterior-anterior current direction for the conditioning stimulus to somatosensory areas and test stimulus to primary motor cortex (M1) using dual-site transcranial magnetic stimulation in the left hemisphere. ***B*** Locations of anatomical S1 (Talairach Coordinates, (TC) based on Talairach atlas; x = -22.31, y = −45.02, z = 54.75) and M1 (TC; x = -17.82, y = 14.99, z = 58.09) stimulation sites in 3-D brain of a representative participant.

0.5–2.0 mV range The group mean (±SD) MSO to evoke ~1.25 mV MEPs was 69.56% (±10.27%). All SICI experiments were conducted at rest except for *Experiment 4b*. CS intensities and ISIs are described below for each experiment.

Experimental design

Experiment 1 – CS intensity recruitment curve for ipsilateral somatosensory-M1 interactions

To evaluate the effects of conditioning stimulus (CS) intensity on somatosensory-M1 interactions, we measured two inter-stimulus intervals (ISIs) of 1 and 2.5 ms using ten different CS intensities between 50 and 120% of M1 active motor threshold (AMT) at 10% increments, as well as 140% and 160% M1 AMT. Each CS intensity was studied in a separate block. In each block, 10 trials for each ISIs of 1 ms, 2.5 ms and test stimulus (TS) alone (total 30 trials) were collected in random order. The order of the 10 blocks of different CS intensities was counterbalanced across participants. Therefore, a total of 300 trials were collected across the 10 blocks of different CS intensities (50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 140% and 160% AMT) with 30 trials in each block. A two-way repeated measures (RM) ANOVA was used to examine the effects of CS intensity (50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 140%, and 160% AMT) on somatosensory-M1 interactions at different ISIs (1 ms, 2.5 ms or TS alone) on raw MEP amplitudes. All data was checked for normality using the Shapiro-Wilk test prior to conducting the RM-ANOVA. If data was non-normally distributed, a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Tukey's post hoc analysis (using q statistic) was used to determine significant differences between any CS intensities at 1 or 2.5 ms ISIs compared to TS alone. To further explore differences between CS intensities and ISI, a two-way RM-ANOVA using MEP amplitudes normalized to TS alone was conducted. Tukey's post hoc analysis was used to investigate significant main effects with more than two factors or interaction effects. A total of 16 volunteers (10 females, mean age 28.2 ± 4.5 years, range 20–38 years) were included in the primary analysis. In addition, we tested an additional block at 180% M1 AMT CS intensity in a subset of participants (n = 10) who had low AMT. For this additional collection, a one-way RM-ANOVA was performed with the factor ISI to evaluate if raw MEP amplitudes at either 1 or 2.5 ms ISIs were different compared to TS alone for the 180% CS intensity. Tukey's post hoc analysis was used to measure confirm specific differences between 1 and 2.5 ms ISI compared to TS alone.

Experiment 2 – Time-course of somatosensory-M1 interactions at supra-threshold CS intensity and AMT measured at somatosensory stimulation location

To evaluate the time-course of ipsilateral somatosensory-M1 interactions at a supra-threshold conditioning stimulus (CS) intensity, ds-TMS was measured at seven inter-stimulus intervals (ISIs) of 1, 2, 2.5, 3, 4, 5, and 6 ms. These specific ISIs were determined based on previous ds-TMS work [7,9–12,15–28], our Pilot Experiment (see *Supplemental Material*) in addition to specific hypotheses related to short-latency afferent inhibition (SAI) (1 ms) and SICI (2.5 ms). This experiment was conducted to evaluate whether somatosensory-M1 inhibition discovered in *Experiment 1* at higher CS intensities could also be measured a longer ISIs. CS intensity was set to a supra-threshold intensity of 160% of M1 active motor threshold (AMT). In two subjects, 160% M1 AMT was greater than the maximum stimulator output and therefore 140% M1 AMT was used. Twelve trials were collected at each of the seven ISIs and with test stimulus (TS) alone in random order over two blocks of 48 trials. Therefore, a total of 96 trials were collected across the two blocks (n = 12 for each condition: TS alone, 1, 2, 2.5, 3, 4, 5 and 6 ms ISIs). A one-way RM-ANOVA was used to examine the effects of ISI on somatosensory-M1 interactions with raw MEP amplitudes. All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Tukey's post hoc analysis (q statistic) was used to determine significant differences between any ISI with TS alone. To

further analyze the differences between ISIs, a separate one-way RM-ANOVA using MEP amplitudes normalized to TS alone was conducted. Tukey's post hoc analysis was used to determine significant differences between any ISI. Data from the same 16 volunteers from *Experiment 1* were included in the analysis.

In addition, to measure the degree of current spread from the somatosensory stimulation location to M1, AMT was measured over the somatosensory stimulation location (somatosensory-AMT) using the same protocol for AMT over M1. In separate blocks, a 2.5 cm coil was placed at the somatosensory stimulation location and somatosensory-AMT was measured, when possible. These values are reported in Table 2. The ratios of somatosensory-AMT to M1-AMT were used to estimate the stimulation intensities needed at the somatosensory location to match stimulation at M1 (see Table 2). When somatosensory-AMT was not measurable (>100%), a value of 100% of stimulator output was assigned to somatosensory-AMT to calculate the ratio. Therefore, this ratio reflects the most conservative ratio whereas the real values are higher.

Experiment 3 — CS intensity recruitment curve for SICI and time-course of SICI

Due to the potential of current spread from the somatosensory stimulation location to M1 and potential activation of SICI circuitry, we evaluated SICI in the same participants. This experiment was conducted to evaluate whether the dependence of SICI on CS intensity was different from somatosensory-M1 CS intensity relationship calculated in *Experiment 1* in the same participants. In addition, the CS intensity of peak SICI inhibition could be used in correlational analyses (see below) with peak somatosensory-M1 inhibition. In the first part of the experiment, SICI recruitment curves for conditioning stimulus (CS) intensity were measured at inter-stimulus intervals (ISIs) of 1 and 2.5 ms (the same ISIs used in *Experiment 1* for ds-TMS) with CS intensities between 50 and 120% of M1 active motor threshold (AMT) at 10% increments. Ten trials were collected for each condition at 1 ms, 2.5 ms ISIs and test stimulus (TS) alone (total 30 trials) for each CS intensity in random blocks. The order of the 8 blocks at different CS intensities (30 trials in each block) was counterbalanced across participants. Therefore, a total of 240 trials were collected across the 8 blocks (CS intensities of 50%, 60%, 70%, 80%, 90%,100%, 110% and 120% AMT). A two-way RM-ANOVA with factors ISI and CS intensity was used to examine the effects of ISI on SICI interactions using raw MEP amplitudes. All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Tukey's post hoc analysis (q statistic) was used to evaluate significant differences between any ISI and TS alone. To further evaluate differences between ISI and CS intensity, MEP amplitudes were normalized to TS alone, and a second two-way RM-ANOVA was conducted. Tukey's post hoc analysis (q statistic) was used to evaluate significant main and interaction effects. In the second part of the experiment, the time-course of SICI was measured with ISIs 1, 2, 2.5, 3, 4, 5 and 6 ms with CS intensity of 90% M1-AMT. This experiment was conducted to evaluate whether the dependence of SICI on ISI was different from somatosensory-M1 ISI relationship calculated in *Experiment 2* in the same participants. The same 16 volunteers who participated in *Experiments 1 and 2* were included in the analysis. Twelve trials were delivered in random order at each of the seven ISIs and with TS alone in two blocks of 48 trials. Therefore, a total of 96 trials were collected across the 2 blocks ($n = 12$ for condition: TS alone, ISIs of 1 ms, 2 ms, 2.5 ms, 3 ms, 4 ms, 5 ms and 6 ms). All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. A one-way RM-ANOVA was used to examine the effects of ISIs on SICI with raw MEP amplitudes. Tukey's post hoc analysis was used to evaluate significant differences at any ISI compared to TS alone. To further examine differences between ISIs, MEP amplitudes were normalized to TS alone, and second one-way RM-ANOVA was performed. Tukey's post hoc analysis was used to evaluate significant differences between ISIs.

We also performed Pearson correlations to determine if the individual amount of inhibition for somatosensory-M1 and SICI correlated. The degree of somatosensory-M1 inhibition in *Experiment 2* and SICI in *Experiment 3* during the time-course experiments were used for the correlations, which represented somatosensory-M1 inhibition using 160% CS intensity and SICI using 90% CS intensity. We also correlated somatosensory-M1 inhibition in *Experiment 1* and SICI in *Experiment 3* during the recruitment curve testing at 1 and 2.5 ms ISIs. Here, we correlated somatosensory-M1 inhibition at 140% M1 AMT to SICI at 70% M1 AMT as well as 160% M1 AMT to 80% M1 AMT since our calculated current spread ratios suggested that somatosensory stimulation would need to be approximately 2 times that of M1. Pearson's correlation was also performed to determine if the amount of somatosensory-M1 inhibition correlated with the proximity between actual somatosensory stimulation site to the anatomical S1 location as well as distance between M1 and somatosensory stimulation sites. The distances between sites were measured as the Euclidian distance using the 3-dimensional TC for each individual using the formula:

Euclidian distance between S1 anatomical and somatosensory stimulation sites $= \sqrt{((ax - sx)^2 + (ay - sy)^2 + (az - sz)^2)}$

The x, y and z S1 anatomical or M1 stimulation site TC are represented by ax, ay and az. The x, y and z S1 stimulation site TC are represented by sx, sy and sz. Finally, we correlated the amount of somatosensory-M1 inhibition in *Experiments 1* and *2* with 160% CS intensity at 1 ms ISI to determine if there was an association between repeated measures as this would provide a measure of test re-test reliability [60].

We also collected somatosensory-AMT using the larger 40 or 50 mm coils. These values were used to calculate the ratio difference between somatosensory-AMT and M1-AMT (see Table 3). Like Experiment 1, when no somatosensory-AMT was measurable, a value of 100% of stimulator output was used for somatosensory-AMT to calculate the ratio. Therefore, this ratio reflects a conservative ratio whereas the real values are higher.

Table 2
Individual M1 and somatosensory active motor threshold (AMT) as well as current spread ratio measured with 2.5 cm diameter coils.

Participant	M1-AMT	Somatosensory-AMT	Current Spread Ratio (somatosensory-AMT/M1-AMT)
1	61	96	1.57
2	61	>100	1.64
3	55	>100	1.82
4	59	>100	1.69
5	44	>100	2.27
6	45	92	2.04
7	44	76	1.73
8	54	>100	1.85
9	51	>100	1.96
10	41	>100	2.44
11	47	>100	2.13
12	71	>100	1.41
13	61	>100	1.64
14	54	86	1.59
15	62	>100	1.61
16	70	>100	1.43

Table 3
Individual M1 and somatosensory active motor threshold (AMT) and current spread ratio measured with 4.0/5.0 cm diameter coils.

Participant	M1-AMT	somatosensory- AMT	Current Spread Ratio (somatosensory-AMT/M1-AMT)
1	47	95	2.02
2	47	>100	2.13
3	50	80	1.60
4	57	>100	1.75
5	40	>100	2.50
6	37	71	1.92
7	33	66	2.00
8	46	>100	2.17
9	36	>100	2.78
10	34	83	2.44
11	35	71	2.03
12	46	>100	2.17
13	45	>100	2.22
14	40	72	1.80
15	46	>100	2.17
16	47	>100	2.13

Experiment 4 — The effects of isometric muscle contraction on somatosensory-M1 interactions and SICI

The effects of isometric muscle contraction (compared to rest) on somatosensory-M1 interactions (*Experiment 4a*) and SICI (*Experiment 4b)* were investigated. During active contraction, participants held a ~20% MVC (in the target FDI muscle). Visual and auditory feedback was provided to ensure consistency with the active contraction. SICI was measured at both 1 and 2.5 ms inter-stimulus intervals (ISIs) with CS of 90% M1-active motor threshold (AMT) and test stimulus (TS) of ~1.25 mV. Somatosensory-M1 interaction was measured at both 1 and 2.5 ms ISIs with CS of 160% M1-AMT and TS of ~1.25 mV. Ten trials for each ISI and TS alone (total of 30 trials) were delivered in random order in separate blocks. SICI and somatosensory-M1 were measured in four separate blocks (rest SICI, rest somatosensory-M1, active SICI, and active somatosensory-M1) in counter-balanced order across participants. Therefore, a total 120 trials were collected for each participant (30 trials for each condition: rest SICI rest somatosensory-M1, active SICI and active somatosensory-M1). Separate two-way RM-ANOVAs with factors ISI (TS alone, 1 ms, 2.5 ms) and condition (rest, active) were used to examine changes in raw MEP amplitudes for somatosensory-M1 (*Experiment 4a)* and SICI (*Experiment 4b*). All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Tukey's post hoc analysis (using the q test statistic) was used to confirm differences between 1 or 2.5 ms to TS alone. To further analyze the differences between ISI (1 and 2.5 ms) and condition (active versus rest), separate two-way RM-ANOVA were used to statistically compare MEP amplitudes normalized to TS alone for somatosensory-M1 (*Experiment 4a)* and SICI (*Experiment 4b*). Tukey's post-hoc analyses (using the q test statistic) were used to measure differences between variables with more than two factors and interaction effects.

Experiment 5 — Interactions between SAI & somatosensory-M1 inhibition

To measure whether somatosensory-M1 inhibition interacted with short-latency afferent inhibition (SAI), somatosensory-M1 inhibition was measured in the presence of SAI. This experiment was conducted to evaluate whether the two different inhibitory somatosensory-motor circuits (SAI and somatosensory-M1) interact with each other. SAI was measured at inter-stimulus intervals (ISIs) of 20, 21, 22 and 23 ms. For SAI, conditioning stimulus (CS) intensity was set at peripheral motor threshold, which was the lowest intensity to elicit a visible thumb twitch using median nerve stimulation at the right wrist. Test stimulus (TS) intensity was set at ~1.25 mV. At each of the 4 SAI ISIs, somatosensory-M1 was measured using ISI of 1 ms with CS intensity of 160% M1-AMT. Ten trials at each SAI ISI, TS alone as well as in presence of somatosensory-M1 were collected in random order. Therefore, a total 90 trials were collected (10 trials for each condition: TS alone, 20 ms SAI, 20 ms SAI in presence of somatosensory-M1, 21 ms SAI, 21 ms SAI in presence of somatosensory-M1, 22 ms SAI, SAI in presence of somatosensory-M1, 23 ms SAI, 23 ms SAI in presence of somatosensory-M1). A one-way ANOVA was used to examine the amount of SAI with the factor ISI (TS alone, 20, 21, 22, 23 ms) using raw MEP amplitudes. All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Tukey's post hoc analysis (using q statistic) was used to compare SAI at each ISI relative to TS alone. Furthermore, the MEP amplitudes were normalized to TS alone and a one-way ANOVA was used to investigate differences between ISIs. Tukey's post-hoc analyses (using q statistic) were used to measure the effects at each conditioned ISIs. To calculate the amount of change of SAI when somatosensory-M1 inhibition was present, the % of SAI in presence of somatosensory-M1 inhibition was calculated relative to the SAI alone at each given SAI ISI. Separate two-way ANOVAs were used to statistically compare the % SAI MEP amplitudes changed in presence of somatosensory-M1 with the factor ISI (20, 21, 22, 23 ms) and somatosensory-M1 interaction (present or absent). Tukey's post-hoc analyses (using q statistic) were used to further test the effects at each conditioned ISI relative to each other.

Experiment 6 — Interactions between SAI & SICI

Short-latency afferent inhibition (SAI) and SICI interactions were measured. This experiment was conducted to evaluate whether the two different inhibitory circuits (SAI and SICI) interact, and whether their interaction was different than the interactions between SAI and somatosensory-M1 measured in *Experiment 5*. SAI was measured at inter-stimulus intervals (ISIs) of 20, 21, 22 and 23 ms. For SAI, conditioning stimulus (CS) intensity was set at peripheral motor threshold, which was the lowest intensity to elicit a visible thumb twitch using median nerve stimulation at the right wrist. Test stimulus (TS) intensity was set to result in ~1.25 mV MEP amplitude. At each of the 4 SAI ISIs, SICI was measured at an ISI of 1 ms using a CS intensity of 90% M1-AMT. Ten trials at each SAI ISI, TS alone as well as in presence of SICI were collected in random order. Therefore, a total 90 trials were collected (10 trials for each condition: TS alone, 20 ms SAI, 20 ms SAI in presence of SICI, 21 ms SAI, 21 ms SAI in presence of SICI, 22 ms SAI, 22 ms SAI in presence of SICI, 23 ms SAI, 23 ms SAI in presence of SICI). A one-way RM-ANOVA was used to evaluate the amount of SAI with the factor ISI (TS alone, 20, 21, 22, 23 ms) using raw MEP amplitudes. All data was checked for normality using the Shapiro-Wilk test. If data was non-normally distributed, then a Box-Cox transformation [59] was performed and the transformed data was used in the RM-ANOVA. Furthermore, the MEP amplitudes were normalized to TS alone and a one-way RM-ANOVA was used to investigate differences between ISIs. Tukey's post-hoc analyses (using the q test statistic) were used to measure differences between conditioned ISIs. To calculate the effects of SICI on SAI, the % of SAI in presence of SICI was calculated relative to SAI alone at each given SAI ISI. A two-way RM-ANOVA was used to compare % SAI in presence of SICI with the factor ISI (20, 21, 22, 23 ms) and SICI (present or absent). Tukey's post-hoc analyses (using q statistic) were used to further test the effects at each conditioned ISI relative to each other.

Somatosensory stimulation location compared to S1 anatomical location

To measure whether statistical differences existed between S1 anatomical and somatosensory stimulation sites, a two-way RM ANOVA using factors somatosensory location (S1 anatomical, somatosensory stimulation locations) and Talairach coordinate (x,y,z) from Talairach atlas was conducted on all 29 participants that were used in analyses for Experiments 1–6. Tukey's post hoc analysis (q statistic) was used to examine if differences existed for the x, y or z coordinates between S1 anatomical or somatosensory stimulation location. A Pearson's product moment correlation was also conducted to investigate the association between the somatosensory stimulation Euclidian distance (mean distance between mean somatosensory stimulation location and actual somatosensory stimulation location) and the % of somatosensory-M1 (at 1 ms ISI with 160% AMT). For participants in Experiments 1 and 2, the % of somatosensory-M1 was calculated as the mean % somatosensory-M1 inhibition from Experiments 1 and 2. For participants in Experiments 4 and 5, % of somatosensory-M1 inhibition was taken from % somatosensory-M1 inhibition at rest with 1 ms ISI and 160% AMT.

Results

Somatosensory stimulation location compared to S1 anatomical locations: relationship with somatosensory-M1 inhibition

Two-way RM-ANOVA based on S1 anatomical and somatosensory stimulation locations revealed significant main effects of somatosensory location ($F(1,28) = 10.82$, $p = 0.003$), coordinate ($F(2,56) = 1090.30$, $p = 0.0000001$) and a significant interaction between somatosensory location x coordinate ($F(2,56) = 14.55$, $p = 0.0000001$). Tukey's post hoc analysis revealed that the somatosensory stimulation locations were significantly more negative (more posterior) in the y coordinate direction ($p = 0.0001$) but not in x or z coordinate directions with a mean difference of 9.14 mm ($n = 29$, mean S1 anatomical y coordinate = −33.73, mean somatosensory stimulation location = −42.87) ($p < 0.05$) (see Supplemental Figs. 2 and 3).

Pearson's correlational analysis between somatosensory Euclidian distance and somatosensory-M1 inhibition was not significant ($n = 29$, $r = -0.27$, $p = 0.16$). Furthermore, we also evaluated whether individual somatosensory stimulation y coordinate locations was significantly different associated amount of somatosensory-M1 inhibition (at 1 ms with 160% CS intensity) using a Pearson correlational analysis. However, there was no significant association between somatosensory stimulation y coordinate and somatosensory-M1 inhibition ($n = 29$, $r = 0.28$, $p = 0.28$).

Experiment 1 –CS intensity recruitment curve for ipsilateral somatosensory-M1 interactions

Two-way RM-ANOVA on absolute MEP amplitudes found significant main effects of CS intensity ($F(9,126) = 5.23$, $p = 0.000005$) and ISI ($F(2, 28) = 9.97$, $p = 0.0005$) as well as a significant interaction between CS intensity and ISI ($F(18, 252) = 3.83$, $p = 0.000001$). Tukey's post hoc analysis confirmed that MEPs were significantly inhibited at conditioned 1 ms relative to unconditioned TS alone ($p = 0.0005$). Two-way RM-ANOVA with the normalized MEP data confirmed significant main effects of CS intensity ($F(9,126) = 7.15$, $p = 0.000001$), ISI ($F(1,14) = 21.70$, $p = 0.0004$) as well as a significant interaction between CS intensity and ISI ($F(9,126) = 3.82$, $p = 0.0003$). Normalized MEP amplitudes were smaller at 1 ms compared to 2.5 ms. Furthermore, normalized MEP amplitudes were lowest at 160% CS intensity regardless of ISI. Tukey's post-hoc analysis confirmed significantly more inhibited MEPs at 140% relative to 50% ($p = 0.0003$), 60% ($p = 0.0001$), 80% ($p = 0.001$) and 100% ($p = 0.03$) at M1-AMT CS intensities and 160% compared to 50–120% ($p = 0.00004$) CS intensities for 1 ms ISI. For 2.5 ms ISI, normalized MEPs were significantly more inhibited at 160% relative 50% ($p = 0.001$), 60% ($p = 0.003$), 70% ($p = 0.008$), 80% ($p = 0.001$), and 100% ($p = 0.005$) CS intensities. Finally, normalized MEP amplitudes were more inhibited at 160% CS intensity at 1 ms compared to 2.5 ms ISI (Fig. 2a). In a separate analysis using one-way RM-ANOVA on the subset of participants ($n = 10$) tested at 180% M1 AMT CS intensity, the main effect of ISI was significant ($F(2,18) = 10.16$, $p = 0.002$) (Fig. 2b). Tukey's post-hoc analysis confirmed that MEP amplitudes were inhibited at 1 ms ($p = 0.009$) and 2.5 ms ($p = 0.004$) ISIs compared to the unconditioned TS alone.

Experiment 2 -– Time-course of somatosensory-M1 interactions at supra-threshold CS intensity (160% M1 AMT) and AMT measured at somatosensory stimulation location

One-way RM-ANOVA on absolute MEP amplitudes revealed a significant main effect of ISI ($F(7,105) = 4.99$, $p = 0.00007$). Tukey's post-hoc analysis showed that raw MEP amplitudes were significantly decreased at ISI of 1 ms relative to TS alone ($p = 0.0002$). MEP amplitudes at ISI of 2.5 ms were not significantly different from TS alone ($p = 0.64$). Using normalized MEP amplitudes, the one-way RM-ANOVA also found a significant main effect of ISI ($F(6,90) = 9.75$, $p < 0.00001$). Tukey's post hoc analysis found that MEP amplitudes were more inhibited at 1 ms ISI compared to 2 ($p = 0.0001$), 2.5 ($p = 0.0008$), 3 ($p = 0.0001$), 4, ($p = 0.0003$), 5 ($p = 0.0001$) and 6 ($p = 0.0001$) ms ISIs (Fig. 3).

The individual results for M1-AMT, somatosensory-AMT and calculated somatosensory-AMT/M1-AMT ratio are displayed in Table 2. Somatosensory-AMT could only be measured in 4 out of 16 participants when using the small 2.5 cm coils. The mean somatosensory-AMT/M1-AMT ratio was 1.80 (range 1.41–2.44) suggesting that stimulation at somatosensory stimulation location had to be about double the stimulation intensity of M1 to produce equivalent activation in the ipsilateral M1.

Experiment 3– CS intensity recruitment curve and time-course of SICI

Two-way RM-ANOVA for SICI recruitment curve using absolute MEP amplitudes revealed main effects for CS intensity ($F(7,105) = 11.14$, $p = 0.00000001$) and ISI ($F(2,30) = 114.21$, $p = 0.00000001$) as well as a significant interaction between CS intensity and ISI ($F(14,210) = 13.20$, $p = 0.00000001$). Tukey's post-hoc analysis found that MEP amplitudes were inhibited at 1 ($p = 0.0001$) ms and 2.5 ($p = 0.0001$) ms relative to TS alone. Based on normalized MEP amplitudes, the main effects of CS intensity ($F(7,105) = 17,28$, $p = 0.00000001$), ISI ($F(1,15) = 29.61$, $p = 0.00007$) and interaction between CS intensity x ISI ($F(7,105) = 13.80$, $p = 0.000001$) were significant. Overall, normalized MEP amplitudes were more inhibited at 1 ms compared to 2.5 ms, and at higher CS intensities between 80 and 120% AMT compared to 50 or 60%. Tukey's post hoc analysis confirmed significantly more inhibited MEP amplitudes at 1 ms compared to 2.5 ms ISI at CS intensities 80% ($p = 0.0001$), and 90% ($p = 0.0001$) AMT (Fig. 4).

One-way RM-ANOVA using raw MEP amplitudes for time-course of SICI found a main effect for ISI ($F(7,105) = 31.90$, $p = 0.00000001$). Tukey's post-hoc analysis revealed that MEP amplitudes were inhibited at 1 ($p = 0.0001$), 2 ($p = 0.0001$), 2.5

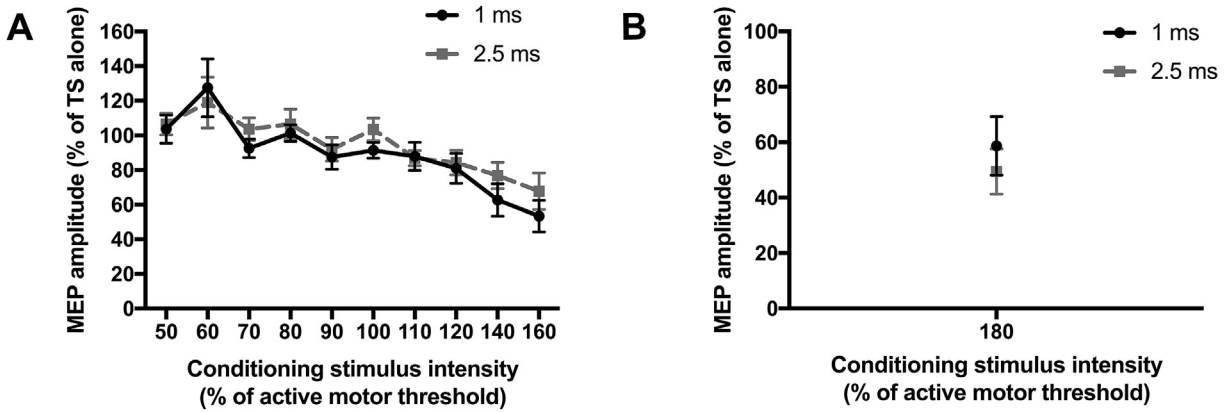

Fig. 2. CS intensity recruitment curve for somatosensory-M1 interactions.
The effects of different somatosensory CS intensities on modulating M1 excitability in Experiment 1 (n = 16) at inter-stimulus intervals (ISI) of 1 and 2.5 ms A across CS intensities 50–120% at 10% intervals, 140% and 160% of AMT, and B 180% CS intensity. Note that somatosensory-M1 interactions at 180% AMT were only collected in a subset of 10 participants. MEP amplitudes are expressed as a percentage of TS alone. Errors bars represent standard error. Results revealed significantly inhibited MEP amplitudes at 1 relative to 2.5 ms ISI at 160% CS intensity, and overall at 140 and 160% CS intensities relative to 60% CS intensity for both ISIs. MEP amplitudes were also inhibited with 180% CS intensities at 1 and 2.5 ms ISIs relative to TS alone.

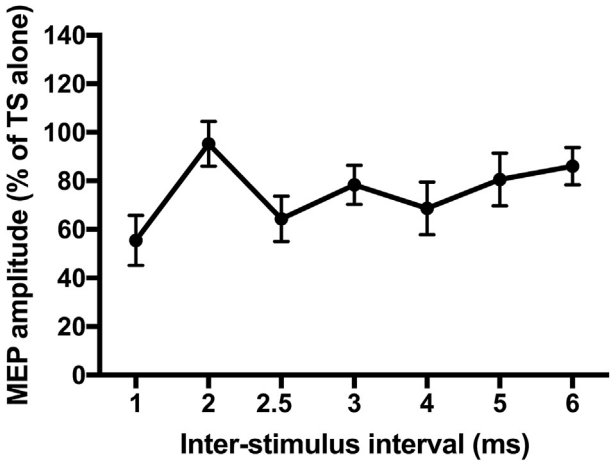

Fig. 3. Time-course of somatosensory-M1 interactions at supra-threshold CS intensity.
The time-course of somatosensory CS on modulating M1 excitability in Experiment 2 (n = 16) using a supra-threshold (160% AMT) CS intensity. MEP amplitudes are represented as percentages of TS alone. Errors bars represent standard error. Results revealed that MEP amplitudes were significantly inhibited at 1 ms relative to 2, 2.5, 3, 4, 5, and 6 ms ISIs.

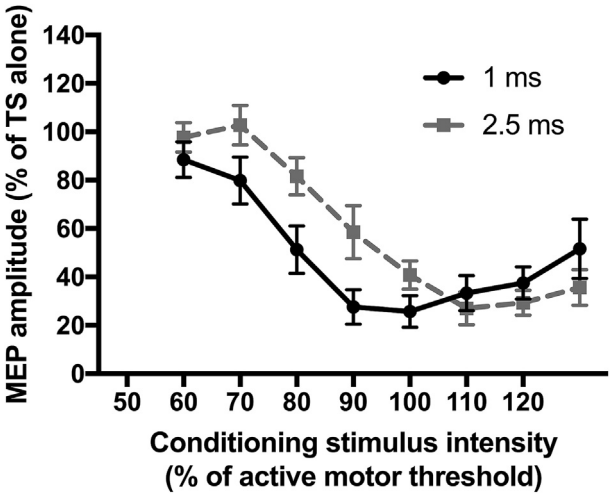

Fig. 4. CS intensity recruitment curve for SICI.
The effects of SICI at various M1 CS intensities in Experiment 3 (n = 16) at ISIs of 1 and 2.5 ms. MEP amplitudes are represented as a percentage of TS alone. Errors bars represent standard error. Results revealed significantly inhibited MEP amplitudes at 1 ms compared to 2.5 ms ISI at 80 and 90% CS intensities.

(p = 0.0001) and 4 (p = 0.04) ms ISIs relative to TS alone. Using the normalized MEP amplitudes, one-way RM-ANOVA found a significant main effect of ISI ($F(6,90) = 33.25$, $p = 0.00000001$). Tukey's post-hoc analysis revealed that normalized MEP amplitudes were more inhibited at 1 ms compared to all other ISIs (2, 3, 4, 5 and 6 ms) (p = 0.00012) ms ISIs. Also, 2 ms ISI normalized MEP amplitudes were more inhibited than 3 (p = 0.0005), 5 (p = 0.01), and 6 (p = 0.0002) ms ISIs while 2.5 ms were more inhibited compared to 3 (p = 0.0005), 5 (p = 0.01) and 6 ms (p = 0.0002) (Fig. 5).

The results for somatosensory-AMT with larger diameter 4 or 5 cm coils are shown in Table 3. Less than half of the participants (7 out of 16) revealed a somatosensory-AMT even with the larger diameter coils. The mean somatosensory-AMT to M1-AMT ratio was 2.11 (range 1.60–2.78) supporting the results of Experiment 2 that stimulation at somatosensory areas had to occur at about double the stimulation intensity of M1 to produce similar cortical activation in ipsilateral M1.

Pearson correlations revealed a significant association between the amount of inhibition measured in *Experiments* 1 and 2 with somatosensory-M1 ds-TMS at 1 ms with 160% AMT CS intensity (n = 14, r = 0.52, p = 0.047) (Fig. 6). Somatosensory-M1 interactions in *Experiment 1* at 1 ms (n = 14, r = 0.39, p = 0.14) or 2.5 ms (n = 14, r = 0.36, p = 0.17) did not significantly correlate with SICI (90% SICI vs. 160% CS intensities somatosensory-M1). 1 ms (n = 16, r = 0.36, p = 0.17) or 2.5 ms (n = 16, r = 0.19, p = 0.49) in *Experiment 2* did not correlate with 70% CS intensity SICI (70% for SICI vs. 140% CS intensity for somatosensory-M1) nor did 1 ms (n = 14, r = 0.34, p = 0.19) or 2.5 ms (n = 14, r = 0.34, p = 0.21) at 80% SICI (80% SICI vs. 160% CS intensities somatosensory-M1) from *Experiments 1* and *3*. Furthermore, there were no significant correlations between somatosensory-M1 inhibition in *Experiment 2* (with 160% CS intensity at 1 ms) and Euclidian distances between S1 anatomical and somatosensory stimulation sites (n = 16, r = 0.05, p = 0.85) nor the M1 and somatosensory stimulation sites (n = 16, r = −0.35, p = 0.19).

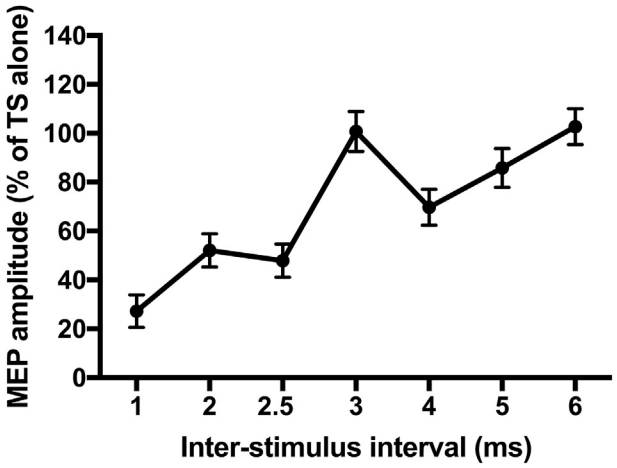

Fig. 5. Time-course of SICI.
The time-course of SICI in M1 in Experiment 3 (n = 16) using 90% AMT CS intensity. MEP amplitudes are represented as a percentage of TS alone. Errors bars represent standard error. Results revealed significantly inhibited MEP amplitudes at 1, 2 and 2.5 ms relative 3, 5, and 6 ms ISIs.

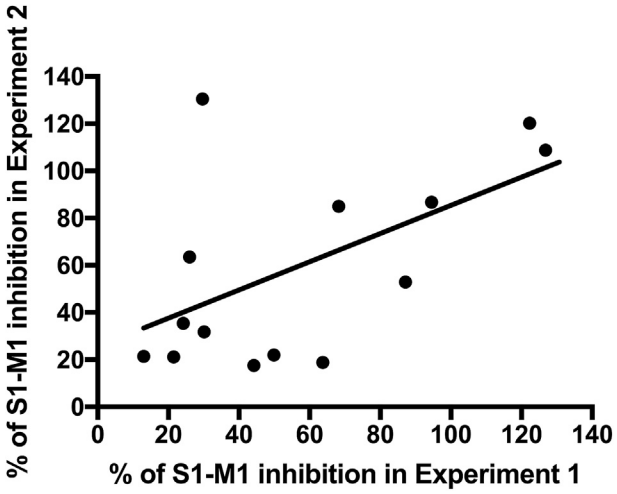

Fig. 6. Correlations between somatosensory-M1 inhibition across experiments.
Relationship between somatosensory-M1 inhibition at 1 ms ISI and 160% CS intensity in Experiments 1 and 2. Each point represents one subject. Somatosensory-M1 inhibition at 1 ms showed significant correlation (n = 14, r = 0.58, $p < 0.05$) across Experiment 1 and Experiment 2.

Experiment 4 – The effects of isometric muscle contraction on somatosensory-M1 interactions and SICI.

In *Experiment 4a,* for somatosensory-M1, two-way ANOVA using raw MEP amplitudes revealed a significant main effect of ISI ($F(2,24) = 9.65$, $p = 0.0008$). Tukey's post-hoc showed that MEP amplitudes were significantly inhibited at both 1 ms ($p = 0.0007$) and, to a lesser extent, 2.5 ms ($p = 0.03$) when conditioned with somatosensory CS compared to TS alone. Two-way RM-ANOVA with normalized MEP data found no main effects of condition ($F(1,12) = 0.12$, $p = 0.73$) or ISI ($F(1,12) = 2.96$, $p = 0.11$) or interactions between ISI and condition (active vs. rest) ($F(1,12) = 0.0089$, $p = 0.93$) (see Fig. 7a).

In contrast, in *Experiment 4b* for SICI, the two-way RM-ANOVA using raw MEP amplitudes for SICI found significant main effects for condition ($F(1,12) = 17.14$, $p = 0.001$), ISI ($F(2,24) = 39.13$, $p = 0.000001$) and a significant interaction between ISI x condition ($F(2,24) = 27.36$, $p = 0.00001$). Tukey's post hoc analysis confirmed that MEP amplitudes were significantly inhibited at 1 ($p = 0.0001$) ms compared to TS alone. Two-way RM-ANOVA with the normalized MEP data further confirmed significant main effects of condition ($F(1,12) = 35,42$, $p = 0.00007$), ISI ($F(1,12) = 31.92$, $p = 0.0001$) and significant interaction between condition x ISI ($F(1,12) = 39.73$, $p = 0.00004$). Tukey's post hoc analyses revealed a greater inhibition at 1 ms compared to 2.5 ms at rest ($p = 0.0002$) but SICI was significantly reduced for both 1 ms ISI ($p = 0.0002$) with active contraction compared to rest (see Fig. 7b).

Experiment 5 – Interactions between SAI and somatosensory-M1 inhibition

Based on raw MEP amplitudes, one-way RM-ANOVA found a significant main effect of ISI ($F(4,36) = 5.08$, $p = 0.002$). Tukey's post hoc confirmed that conditioning MN stimulation decreased MEP amplitudes at 20 ($p = 0.002$) and 21 ($p = 0.01$) ms relative to TS alone. One-way ANOVA with normalized MEP amplitudes did not reveal a significant main effect of ISI ($p = 0.76$), supporting that there were no significant differences in the amount of SAI between ISIs. To further investigate the effects of somatosensory-M1 inhibition on SAI, the two-way RM-ANOVA using normalized MEP amplitudes revealed a significant main effect of ISI ($F(3,27) = 10.99$, $p = 0.00007$). Tukey's post hoc analysis were significantly more inhibited at 20 ms relative to 21 ms ($p = 0.002$) and 23 ms ($p = 0.0009$), and 22 ms relative to 21 ms ($p = 0.006$) and 23 ms ($p = 0.003$) regardless of presence of somatosensoty-M1 inhibition. There was no significant effect of condition ($p = 0.66$) or interaction between condition x ISI ($p = 0.69$) (see Fig. 8a).

Experiment 6 – Interactions between SAI and SICI

One-way RM-ANOVA using raw MEP amplitudes revealed a significant main effect of ISI ($F(4,36) = 3.09$, $p = 0.03$). Tukey's post hoc analysis confirmed reduction of MEP amplitude when conditioned by MN stimulation at 22 ($p = 0.01$) ms ISI compared to TS alone. One-way ANOVA with normalized MEP amplitudes did not find a significant main effect of ISI ($p > 0.05$), indicating that there was no difference in the degree of SAI among the ISI tested. To investigate the interactions between SAI and SICI, two-way RM-ANOVA using normalized MEP amplitudes for SAI revealed a significant main effect of SICI presence ($F(1,9) = 12.68$, $p = 0.006$). These results revealed that regardless of SAI ISI, SAI was increased in presence of 1 ms SICI (Fig. 8b).

Discussion

We found a fast inhibitory cortico-cortical circuit between left somatosensory areas and ipsilateral M1 measured using ds-TMS. Specifically, a significant decrease in M1 excitability, measured by decreased MEP amplitudes occurred when the ipsilateral somatosensory areas was stimulated 1 ms before M1. *Experiments 1 and 2* revealed that this 1 ms inhibitory circuit between somatosensory areas and M1 was intensity-dependent and more readily measured when somatosensory areas were stimulated at supra-threshold intensities of 140 and 160% AMT. This is in contrast to our pilot experiment (*see Supplemental Material*), which suggested that this circuit could be activated with sub-threshold somatosensory stimulation. However, the discrepancy between somatosensory-M1 inhibition with 80% CS intensity (*Pilot Experiment and Experiment* 1) could in part be explained by the individual variability at sub-threshold stimulation intensities. In fact, 6 out of the 16 participants in *Experiment 1* demonstrated decreased MEP amplitudes when conditioned at 80% CS intensity at 1 ms ISI compared to the unconditioned condition.

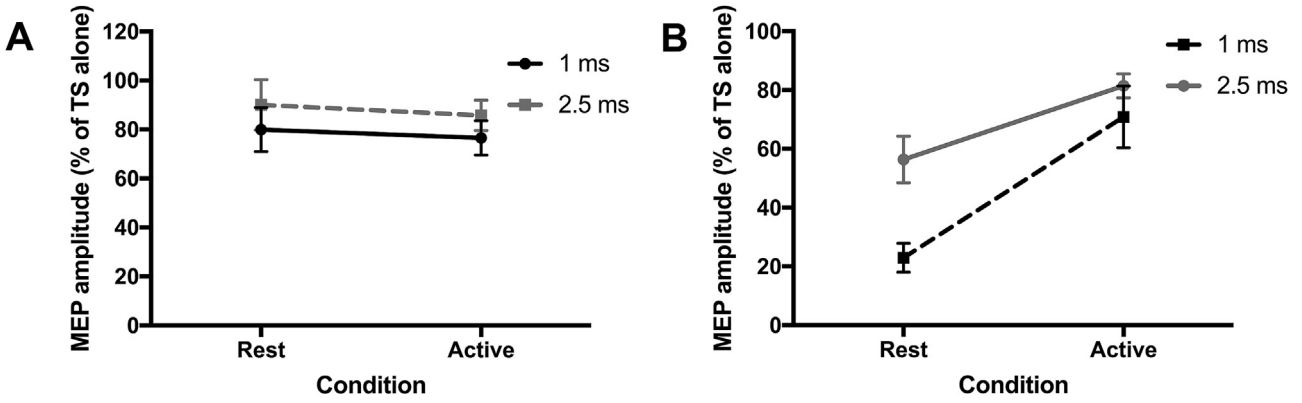

Fig. 7. Effects of target muscle contraction on somatosensory-M1 interactions and SICI.
The effects on isometric contraction of the target first dorsal interosseous (FDI) muscle compared to rest A on the effects of somatosensory-M1 dual-site transcranial magnetic stimulation in Experiment 4. Somatosensory-M1 was measured at inter-stimulus intervals (ISIs) of 1 and 2.5 ms. B SICI was measured at inter-stimulus intervals (ISIs) of 1 and 2.5 ms. Somatosensory-M1 and SICI interactions are expressed as ratios of MEP amplitudes to those of TS alone. Error bars represent standard error. Results revealed no significant differences on somatosensory-M1 interactions between rest and active contraction at either ISI, while SICI was inhibited during active contraction compared to rest, and greater at 1 ms compared to 2.5 ms ISI.

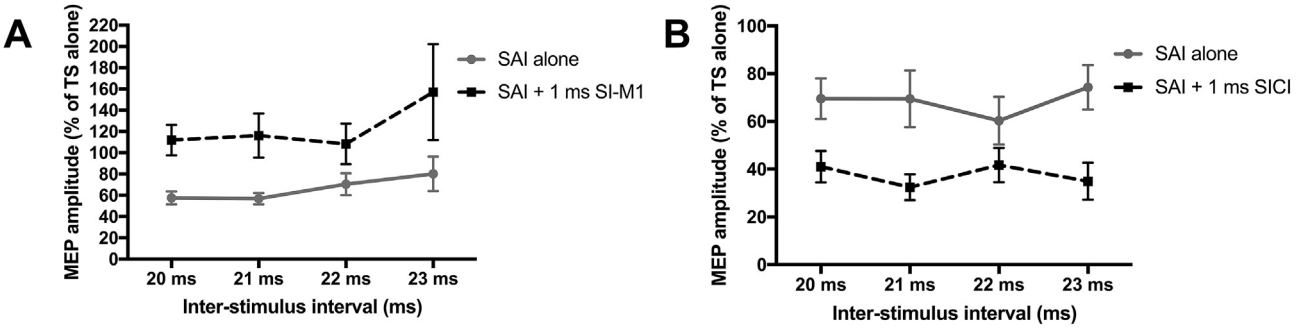

Fig. 8. Effects of somatosensory-M1 inhibition and SICI on SAI.
The interaction between ***A*** somatosensory-M1 dual-site transcranial magnetic stimulation and short-latency afferent inhibition (SAI) in *Experiment 5*. Somatosensory-M1 was measured at an inter-stimulus interval (ISI) of 1 ms. SAI was measured at ISIs of 19–22 ms. ***B*** Interactions between SICI and short-latency afferent inhibition (SAI) in *Experiment 6*. SICI was measured at inter-stimulus intervals (ISI) of 1 ms. SAI was measured at ISIs of 19–22 ms. SAI is expressed as ratios of MEP amplitudes to TS alone. Error bars represent standard error. Results revealed a trend for reduced (disinhibited) SAI regardless of SAI ISI in presence of 1 ms somatosensory-M1 inhibition, while SAI was significantly increased in presence 1 ms SICI regardless of SAI ISI.

Somatosensory-M1 inhibition compared to other ds-TMS studies

S1 is known to be highly connected with the ipsilateral M1 based on both human and animal studies [58,61–64]. Based on architectonic and functional studies, S1 can be divided into 4 areas, Brodmann area (BA) 3a, 3b, 1 and 2, that receive different afferent somatosensory input and send somatotopic projections to M1 [58,61–66]. Tractography studies have also confirmed connections between somatosensory areas in the parietal cortex, including S1, with the ipsilateral M1, and these connections are associated with motor function [67–69]. The somatosensory stimulation location used in the current experiments was targeted to S1 anatomical location near the posterior border of the post-central gyrus, which corresponds to BA2 of S1, an area known to have preferential input from peripheral joint receptors [58,63]. Functionally, this area is known to be involved in hand movements [57], supporting its role in motor control. However, based on our actual stimulation locations (See Table 1), the coil position was often slightly posterior to this location (TC; n = 29; group mean difference; $x = 4.08$ mm, $y = 9.15$ mm and $z = 1.00$ mm) with an average Euclidian distance of 13.46 (±6.51) between S1 anatomical and our actual somatosensory stimulation locations. Not surprisingly, the y coordinate was significantly more posterior for participant's somatosensory stimulation location compared to participant's S1 anatomical location by ~1 cm. However, there was no significant association between somatosensory Euclidian distance (difference between mean somatosensory stimulation location and individualized somatosensory stimulation location) and somatosensory-M1 inhibition. However, we cannot rule out that our stimulation also modulated activity in areas posterior to our anatomical target in BA2. This location likely corresponded to BA5 and/or BA 7 within the superior parietal lobule, which are also involved in somatosensory-motor interactions [70–73]. Although BA2 and BA5 both project to the hand motor region in M1, research in non-human primates has shown that BA2 projects to the caudo-lateral area while BA5 projects to the caudo-medial area [74]. Interestingly, a previous ds-TMS that applied CS to BA5 found increases in MEP amplitudes at 6 ms ISI and decreases at 40 ms ISI during vibrotactile stimulation, but not at rest [28]. The lack of MEP amplitude changes at 6 ms ISI at rest is consistent with our results. However, shorter latency ISIs were not investigated in this study [28]. Therefore, if BA5 was in fact stimulated in our current experiments, it would suggest that the functional connectivity between ipsilateral somatosensory areas and possibly BA5 to M1 may only be active at 1 ms at rest but not at longer ISIs unless performed during a sensory or sensorimotor task. Previous research has shown that conditioning left BA7 prior to ipsilateral M1 stimulation resulted in significant facilitation at 2 ms ISI and 90% RMT CS

intensities [22]. Although the authors did not test 1 ms ISI [22], the facilitation at the shorter ISI is in contrast to the inhibitory effects we found in the current experiments. Therefore, it is unlikely that BA7 stimulation explained the current results.

Several studies have investigated stimulation of ipsilateral PPC, which is an area in relative proximity to our stimulation locations. Facilitation of MEPs at around 4 and 6 ms ISIs at CS intensities of 90% RMT were found while stimulating over P4 electrode location, which corresponded to the posterior part of the posterior parietal sulcus [20,21]. Ds-TMS measurements that systematically targeted CS to anterior intraparietal sulcus (aIPS), central IPS (cIPS) and posterior IPS (pIPS) showed inhibition at 2 ms ISI when targeting the aIPS and facilitation at 8 ms ISI when targeting the cIPS using 90% RMT CS intensities in both left and right hemispheres [23]. Significant inhibition was found at rest with an ISI of 4 ms using either 90% or 120% RMT with CS in the aIPS but not in superior parieto-occipital cortex [27]. Interestingly, facilitation of MEPs at 4 ms ISIs were shown at both aIPS and superior parieto-occipital cortex CS locations when participants performed a grasping task involving transport [27]. Importantly, none of these studies measured PPC-M1 interactions at 1 ms ISI. However, in our experiments, we did not find any effects with ds-TMS at 2, 4 or 6 ms ISIs. This is an important consideration since the IPS, particularly the aIPS, was in relative close proximity to the somatosensory stimulation site used in the current experiments. Therefore, it is unlikely that we were stimulating areas within the PPC known to have functional connectivity with M1 shown using ds-TMS.

To date, a fast 1 ms inhibitory circuit has not been demonstrated by targeting locations outside M1 with ds-TMS. Recently, PMd was shown to facilitate ipsilateral M1 at very short ISIs of 1.2, 2.4, 2.8 and 4 ms at sub-threshold CS intensities using specially designed small ds-TMS coils with CS following TS [10,11]. Therefore, our experiments demonstrate the first evidence of a fast 1 ms inhibitory intra-hemispheric cortico-cortical circuit by applying CS prior to TS.

Relationship between somatosensory-M1 inhibition and other inhibitory cortical circuits

Somatosensory-M1 inhibition was found in the current experiments when we stimulated the somatosensory areas at supra-threshold intensities. This raises the possibility that current spread from our somatosensory stimulation location to M1 might have directly activated M1 SICI inhibitory circuitry. However, it is unlikely that current spread and activation of M1 circuitry was primarily responsible for our current findings based on several observations. First, the strength of somatosensory-M1 inhibition did not correlate with the strength of SICI whereas repeated measurements of somatosensory-M1 inhibition correlated with each other at higher CS intensities. This indicates a lack of association between SICI and somatosensory-M1 inhibition but good reliability in measuring somatosensory-M1 inhibition between sessions, since correlation coefficients can be used as measures of reliability [75]. Second, SICI was found at both 1 and 2.5 ms (*Experiment 3*) whereas somatosensory-M1 inhibition was only reliably detected at 1 ms ISI. These results support previous findings that SICI has two optimal peaks at 1 ms and 2.5 ms ISIs [51,76,77]. It has been suggested that these two peaks of SICI are influenced by different circuits due to their differential influence by voluntary movement and CS intensity [51,76,77]. Third, somatosensory-AMT was measurable only in four participants with the small 2.5 cm coils and only three more participants (7 out of 16) when using larger 4.0/5.0 cm coils. This idea was confirmed as our 'current spread' ratios (see Tables 1 and 2), which were conservatively estimated, suggested it would take two times as much stimulation over somatosensory locations to spread to M1 with the small coils used in the current experiments. Fourthly, there was no significant association between the amount of somatosensory-M1 inhibition and distance between M1 and somatosensory stimulation sites. Additionally, the Euclidian distance from the group mean somatosensory stimulation and individualized somatosensory stimulation locations did not correlate with somatosensory-M1 inhibition. If somatosensory stimulation spread to M1 and activated SICI circuitry, the amount of inhibition would be expected to be related to the proximity to M1. Finally, target muscle contraction decreased 1 ms SICI but had no effect on 1 ms somatosensory-M1 inhibition (*Experiment 4).* The reduction of SICI with active contraction is in line with previous research [51,52], and provides another dissociation between 1 ms SICI and somatosensory-M1 inhibition.

It is relevant to consider these functional findings with previous modelling studies. It is important to keep in mind that the electric field strength is highest at the mid-point of the induced magnetic field (center of the Fig. 8 with our coils) and the electric field strength decreases significantly away from the center [78]. It has been shown that the area of stimulation at 160% of simulator output is ~20 cm^2 with 70 mm figure-of-8 Magstim coils [78]. Clearly, the 70 mm coils are much larger and deliver higher stimulation intensities than the 25 mm coils used in the current experiment. In fact, there is evidence that the electric fields decrease quadratically (not linearly) as distance from the coil increases, and is more drastic for smaller compared to larger TMS coils [79]. Previous research using Finite Element Modelling (FEM) demonstrated that the gyral crowns and lips in the grey matter are most affected by the electric currents when they are perpendicular to the tissue [80]. Therefore, the amount of electric field dispersion and subsequent tissue activation is dependent on the type of tissue in which the electric field is in, how and where the induced electric current activates the appropriate tissue, the actual stimulation parameters, and individual physiological and anatomical factors as reported in M1 experiments [78,80–84]. Therefore, although we cannot rule out that M1 was activated with somatosensory stimulation, the electrical current from somatosensory stimulation would have a) had to disperse and reach M1 from our somatosensory stimulation sites based on the stimulation parameters, and b) hit M1 and activate its tissue at the correct orientation relative to the complex gyrification [84]. Ideally, we would have the means to measure the electric field distribution and strength from stimulation of somatosensory and surrounding areas to know exactly where and how much neural tissue was activated with each somatosensory pulse. However, our functional data supports the notion that direct M1 activation was not a major factor resulting in the somatosensory-M1 inhibition.

Another possible inhibitory circuit that may have been activated by direct somatosensory stimulation is the inhibitory circuit responsible for SAI. SAI is measured when TS after M1 TMS is preceded by a CS to the peripheral MN (or digital) nerve in contralateral upper limb by ~ 21 ms (or N20 + 1 ms) [37]. SAI can be measured over a broader range of ISIs ~20–25 ms after MN stimulation [37,53,85–88]. Due to the known relay latency of peripheral somatosensory input to S1 of ~20 ms via N20 SEPs and M20 SEFs [41–47], somatosensory-M1 cortico-cortical inhibition would occur at ~ 1 ms at the 21 ms SAI latency. Interestingly, we found that SICI increased SAI (*Experiment 6)* while somatosensory stimulation had no significant effect but showed a trend for disinhibition of SAI (*Experiment 5).* Previous research found that SAI (ISI of 23) was disinhibited in presence of SICI at 2 and 3 ms ISIs with CS intensities of 60–90% AMT [53]. The discrepancy between our findings of increased inhibition and previous results of disinhibition with SAI-SICI interactions could be explained by the fact we measured both SAI (19–23 ms) and SICI (1 vs. 2 or 3 ms) at shorter ISIs than the

previous study [53]. SICI at 1 and 2.5 ms are believed to be mediated by different circuits due to the differential influence by voluntary movement and CS intensity [51,76,77]. Regardless, the fact that differential interaction effects on SAI were found in presence of SICI and somatosensory-M1 provides further support of different circuits being responsible for these two inhibitory mechanisms. There is evidence that SAI is at least modulated, if not caused, by direct thalamo-cortical connections [89]. Therefore, it is likely that somatosensory-M1 inhibition and SAI interacted within somatosensory areas causing disinhibition. This finding supports the notion that a fast inhibitory cortico-cortical circuit, represented by somatosensory-M1 inhibition, occurs through monosynaptic connections that exist between somatosensory areas and M1 [90,91]. However, we cannot rule out the possibility of this inhibition could occur through other collateral pathways including the pyramidal tract fibers originating within S1 [92].

The neurotransmitters mediating somatosensory-M1 inhibition are not known. SICI is related to $GABA_A$ receptor [49,93–96] whereas SAI is mediated by a different subtype of $GABA_A$ receptor [94,95]. SAI is also influenced by the cholinergic system since scopolamine, a muscarinic acetylcholine receptor antagonist, decreases SAI [97]. These inhibitory circuits are also modulated by dopamine [98,99]. Interestingly, SAI has been shown to be normal in PD but administration of levodopa reduces SAI [100]. The increased SAI in presence of SICI may be caused by interactions within M1 between different $GABA_A$ receptors or cholinergic inhibitory circuitry involved in SAI. Future research using pharmacological manipulations or patient populations could help clarify the exact mechanisms involved in the novel form of somatosensory-M1 cortico-cortical inhibition as well as interactions between somatosensory-M1, SICI and SAI inhibitory circuits.

The current study had a few limitations that should be highlighted. Different sized coils were used for SICI and somatosensory-M1 ds-TMS due to technical limitations limiting the ability to use the smaller coils for SICI. This could have led to activation of different neuronal populations. However, despite this technical limitation, we were still able to dissociate SICI and somatosensory-M1 suggesting it did not likely have a large effect on the differences between SICI and somatosensory-M1 inhibition at 1 ms. However, previous research has shown subthreshold TMS (without causing an overt MEP) over M1 can influence H-reflexes at short-latencies [101,102]. Therefore, we cannot rule out the possibility that somatosensory stimulation influenced spinal circuitries despite the absence of measurable somatosensory-AMT in most participants. In addition, the amount of 1 ms somatosensory-M1 inhibition at rest was greater in our original sample ($n = 16$) with a mean age of 28.2 years (±4.5 SD) in *Experiments 1–3* compared to second sample ($n = 13$) in *Experiment* 4 with a mean age of 22.8 years (±3 SD). Despite the fact that we found significant 1 ms somatosensory-M1 inhibition in both samples, these findings could suggest that 1 ms somatosensory-M1 inhibition may increase with age. We did not systematically analyze this but it would be interesting work for future research. We used parametric statistical tests after Box-Cox transformations to analyze our data when it was non-normally distributed. This method of Box-Cox transformation is similar to previous TMS experiments using log transformations of non-normal data [88,103]. We chose to use Box-Cox transformations and use parametric tests since non-parametric tests, including Friedman's and Kendall's, are not ideal for two-way repeated measures ANOVA designs. Also, there is evidence that parametric ANOVA tests may be robust enough to deal with violations of normality [104]. And, finally, as mentioned above, our somatosensory stimulation sites were ~1 cm more posterior than our anatomical S1 locations. We did not find a correlation between the somatosensory Euclidean distance and amount of somatosensory-M1 in our participants. This suggests that even if conditioning stimulation occurred at a location more posterior than our targeted S1 anatomical locations it did not result in different degree of somatosensory-M1 inhibition. However, it is important to consider that BA5 and BA7 could have also been activated by somatosensory stimulation in addition to S1. However, it is unlikely that our results can be explained by activating BA7, as previous ds-TMS research has found facilitation rather than inhibition at 2 ms with left BA7-M1 stimulation [22]. Regardless, both BA5 and BA7 areas are involved in somatosensory-motor interactions, and collectively supports the notion that somatosensory areas can inhibit M1 at very short latencies (1 ms).

Conclusions

Stimulation of somatosensory areas, including S1, reliably inhibits MEPs evoked by ipsilateral M1 stimulation at 1 ms ISI at supra-threshold stimulation intensities. Despite the close-proximity between somatosensory areas and M1, our findings (i.e. somatosensory-AMT and correlational analyses) suggest that this is not due to somatosensory stimulation activating M1 SICI circuitry. This notion is corroborated by the finding that SICI but not somatosensory-M1 is reduced during target muscle contraction, while SAI is disinhibited in presence of somatosensory-M1 inhibition but SAI is increased is presence of SICI. Therefore, the current findings identified a novel, fast cortico-cortical inhibitory circuit at 1 ms ISI between somatosensory areas and M1. This novel circuit could provide a new measure to investigate somatosensory-motor connectivity during different motor tasks and in patient populations with sensorimotor deficits.

Conflicts of interest

There were no competing or conflicts of interests for any authors.

Authors contributions

Experiments 1–3 were performed at the Krembil Research Institute at Toronto Western Hospital while Experiments 4–6 were performed at University of Lübeck. *MJNB, AW, MV,* and *RC* conceived the study design. *MJNB, AW, MGP, CG, and JB* acquired the data. *MJNB* analyzed the data. *MJNB, AW, MGP, MV, JB, TB, AM* and *RC* interpreted the data. *MJNB* drafted the manuscript. *MJNB, AW, MGP CG, MV, JB, TB, AM* and *RC* revised the manuscript. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.04.009.

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