Effects of short-latency afferent inhibition on short-interval intracortical inhibition

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Udupa K, Ni Z, Gunraj C, Chen R. Effects of short-latency afferent inhibition on short-interval intracortical inhibition. J Neurophysiol 111: 1350–1361, 2014. First published December 18, 2013; doi:10.1152/jn.00613.2013.—Peripheral nerve stimulation inhibits the motor cortex, and the process has been termed short-latency afferent inhibition (SAI) at interstimulus intervals (ISIs) of ~20 ms. The objective of the present study was to test how SAI interacts with short-interval intracortical inhibition (SICI) under different stimulation conditions. We studied 20 healthy volunteers. Surface electromyogram was recorded from the first dorsal interosseous muscle. Using paired- and triple-pulse paradigms, we investigated how SAI interacts with SICI under these different conditions. The effects of different conditioning stimulus (CS) intensities (0.6–0.9 active motor threshold), SAI latencies (23 and 25 ms), and ISIs (2 and 3 ms) for SICI were examined in rest and active conditions. SAI had inhibitory interactions with SICI at different CS intensities for rest or active SICI, at SAI latencies of 23 and 25 ms. This interaction occurred at weak CS intensities for SICI when there was no inhibition, and SICI became facilitatory in the presence of SAI. This can be explained by SICI inhibiting SAI and not by saturation of inhibition. The interaction between SAI and SICI was greater for SICI at ISI of 3 ms than for ISI of 2 ms, suggesting that different circuits may be activated at these ISIs. We conclude that SAI and SICI have inhibitory interactions that are influenced by factors such as ISI and muscle activities, which should be considered in design and interpretation of cortical interaction studies.

median nerve stimulation; paired-pulse inhibition; short afferent inhibition; short-interval intracortical inhibition; transcranial magnetic stimulation

THERE ARE COMPLEX INTERACTIONS between various intracortical inhibitory and facilitatory circuits in the motor cortex, and these interactions can be studied with transcranial magnetic stimulation (TMS) (Chen 2004; Ni et al. 2011). Understanding of these interactions will help to improve our knowledge of motor cortical physiology and how it is altered in neurological diseases. Inhibition of the primary motor cortex (M1) from peripheral nerve stimulation (Classen et al. 2000; Tokimura et al. 2000) depends on the interstimulus intervals (ISIs) between the sensory stimulus and TMS to M1. The motor cortex is inhibited by median nerve stimulation (MNS) at the wrist at ISI of ~20 ms (Tokimura et al. 2000), which has been termed short-latency afferent inhibition (SAI) (Sailer et al. 2003). Previous studies (Alle et al. 2009; Stefan et al. 2002) showed that SAI interacts with short-interval intracortical inhibition (SICI). One study (Stefan et al. 2002) observed that MNS at three times sensory threshold applied 25 ms prior to TMS reduced SICI elicited by delivering a conditioning stimulus (CS) 3 ms prior to the test stimulus (TS), measured in the abductor pollicis brevis (APB, median innervated) muscle. Another study (Alle et al. 2009) showed that ulnar nerve stimulation at three times sensory threshold applied at the latency of the N20 somatosensory evoked potential +2 ms and +4.1 ms prior to TMS reduced SICI measured in the abductor digiti minimi (ADM, ulnar innervated) muscle under voluntary contraction.

No previous studies have investigated the interactions between SAI and SICI at the ISI that produced the strongest SAI (~N20 + 3 ms) (Tokimura et al. 2000) in the resting state, which may be considered the baseline condition for these studies. Moreover, studies that demonstrated abnormal SAI in neurological disorders such as Alzheimer’s disease (AD) (Di Lazzaro et al. 2002), Parkinson’s disease (PD) (Sailer et al. 2003), and stroke (Di Lazzaro et al. 2012) were performed under these conditions. The aim of the present study was to examine how SAI, mediated by cholinergic circuits, interacts with γ-aminobutyric acid type A (GABA_A)-mediated SICI. We studied SAI and SICI at different TS intensities and investigated the interactions between these two circuits at different CS intensities and ISIs for SICI and at different ISIs for SAI and the effects of rest versus voluntary contraction. We hypothesized that 1) SAI is mediated by circuits distinct from SICI based on different findings for these circuits in diseases and 2) SAI and SICI have inhibitory interactions, and their interactions are strongly influenced by stimulation conditions such as CS intensities, ISIs for both SAI and SICI, and the state of voluntary contraction.

METHODS

Subjects

We studied 20 right-handed healthy volunteers (2 groups of 10 each; age (sex) of group 1: 33.5 ± 8.9 yr (6 men and 4 women) for experiments 1 and 2; age (sex) of group 2: 37.5 ± 4.8 yr (8 men and 2 women) for experiments 3–6, means ± SD). Some of the results from group 1 subjects have been reported (Udupa et al. 2009). The Edinburgh handedness inventory (Oldfield 1971) was used to evaluate handedness, and all the subjects were right-handed. Written informed consent was obtained from all subjects. The protocol was approved by the University Health Network Research Ethics Board in accordance with the Declaration of Helsinki on the use of human subjects in experiments.
Median Nerve Stimulation

MNS was applied at the right wrist by a Digitimer DS7A constantcurrent stimulator (Digitimer, Welwyn Garden City, UK; pulse width 0.2 ms) with standard bar electrodes. The cathode was positioned proximally. Stimulus intensity was adjusted to produce a slight thumb twitch (Abbruzzese et al. 2001), which was 2.68 ± 0.65 times the perceptual threshold.

$N_{20}$ Recording

Subjects relaxed in a comfortable chair. Cup electrodes with conducting gel were placed at C3 (centroparietal contralateral) with Fz (frontal) as the reference (International 10-20 System). MNS was applied at the right wrist at 2 Hz. The latency of the $N_{20}$ component of somatosensory evoked potential was determined by averaging 200 trials. ISIs between MNS and TMS in the experiments were either fixed at 25 ms (SAI25) or set at $N_{20}$ latency + 3 ms (SAI23) (Di Lazzaro et al. 2002). $N_{20}$ + 3 ms (SAI23) was found to produce maximum SAI (Tokimura et al. 2000). SAI23 was chosen because it is widely used in experiments for paired associative stimulation (PAS) (Stefan et al. 2000).

Electromyographic Recording

Surface electromyogram (EMG) was recorded from the right first dorsal interosseous (FDI) muscle with 9-mm-diameter Ag-AgCl electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. The signal was amplified (1,000×), band-pass filtered (2 Hz to 2.5 kHz, Intronix Technologies model 2024F, Bolton, ON, Canada), digitized at 5 kHz by an analog-to-digital (A/D) interface (Micro1401, Cambridge Electronics Design, Cambridge, UK), and stored in a computer for off-line analysis. The EMG signal was monitored on a computer screen and via loudspeaker to provide feedback on the state of muscle relaxation. The subjects relaxed throughout the study except during the experiment with voluntary contraction. For experiments performed at rest, trials contaminated with voluntary muscle activities were rejected.

Transcranial Magnetic Stimulation

TMS was performed with a 7-cm figure-of-eight coil, four Magstim 200 stimulators, and three Bistim modules (Magstim, Whitland, UK) arranged in pyramid system. The outputs of two Magstim 200 stimulators were directed to each of two Bistim modules. The outputs of these Bistim modules were directed to the third Bistim module. The stimulating coil was connected to the third Bistim module. The area for eliciting the best motor response in the right FDI muscle was established over the left M1 (optimal position) with the coil held ~45° to the midsagittal line (approximately perpendicular to the central sulcus). The direction of the induced current was from posterior to anterior and was optimal to activate the corticospinal neurons transsynaptically (Kaneko et al. 1996; Werhahn et al. 1994). The optimal position was marked on the scalp to ensure identical placement of the coil throughout the experiment.

Study Design

We studied the interactions between SAI and SICI in five experiments with two groups of subjects (group 1: experiments 1 and 2; group 2: experiments 3–6). In experiment 1, we tested the effect of three different TS intensities on SAI and SICI. In experiments 2–6, we studied the SAI-SICI interactions at specific parameters specified below. Each trial consisted of one or more CS (MNS or TMS) followed by a suprathreshold TS. The CS elicited by TMS was used to elicit SICI (Kujirai et al. 1993). The test conditions are shown in Table 1.

Experiment 1: Effects of Different Test Stimulus Intensities on SICI and SAI

The TS intensity was labeled according to the test motor evoked potential (MEP) amplitudes it produced. The minimum stimulus intensity that produced MEPs of >1 mV peak-to-peak amplitude in at least 5 of 10 trials was named TS1mV. Stimulus intensities of TS0.2mV and TS2mV were defined in a similar way. We tested different TS intensities while keeping the CS the same. Each run consisted of three different conditions: TS alone, CS2 (CS given 2 ms prior to TS)-TS, and MNS33 (MNS given 23 ms prior to test to generate SAI23)-TS. The test conditions were delivered in random order and repeated 10 times. The intertrials intervals were 6 s. The three different TS intensities were studied in separate runs. In each run long-interval intracortical inhibition (LIIC) and intracortical facilitation were also studied, but the results are not reported here as they are unrelated to the present study.

Experiment 2: Interactions Between SAI and SICI (SAI23, SICI with CS2 and 0.8 resting motor threshold at rest)

MNS was applied at three times the sensory threshold at $N_{20}$ + 3 ms prior to TMS. SICI was elicited with CS at 80% resting motor threshold (RMT, defined as the minimum stimulator output that induced MEPs of >50 μV in at least 5 of 10 consecutive trials with FDI muscle at rest) and 2 ms prior to TS in the relaxed state, termed CS. These parameters were chosen to investigate the interaction between SAI and SICI at their optimal activation (Stefan et al. 2002; Kujirai et al. 1993). Seven test conditions (A–G, Table 1) were delivered in random order and repeated 10 times. TS intensity was either TS1mV or TS1mV MNS23. TS1mV MNS23 refers to TS intensity 1 mV peak-to-peak amplitude in at

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Experiments investigated the effect of short-latency afferent inhibition (SAI) induced by median nerve stimulation (MNS) at 2 different latencies [23 ms for experiments 2–4 and 6 (SAI13) and 25 ms for experiment 5 (SAI3)] on short-interval intracortical inhibition (SICI) at different intensities of conditioning stimulus (CS) given 2 ms prior to test stimulus (TS) (CS2, for experiments 2, 3, 5, and 6) or CS given 3 ms prior to TS (CS3, for experiments 4–6) [X = 0.8 resting motor threshold (RMT) in experiment 2; 0.6–0.9 active motor threshold (AMT) in experiment 3, 0.7 or 0.9 in experiments 4–6 in separate runs]. In conditions A–C the effects of SICI and SAI on 1-mV test motor evoked potential (MEP) were assessed, whereas in conditions D–H TS intensity was increased to produce 1-mV test MEP in the presence of MNS23 (1 mV MNS23). *In experiment 5 TS intensity was increased to produce 1 mV test MEP in the presence of MNS23 (1 mV MNS23). In condition H, a second stimulus ($S_2$) was given 2 or 3 ms (separate runs depending on the CS-ISI used) after TS to check for short-interval intracortical facilitation (SICF) in experiments 3, 4, and 6. MEP amplitude ratios G/I, B/A, and E/D were compared to examine SICI in the presence of SAI and SICI matched for amplitude and intensity, respectively. Similarly, GIE, CIA, and FID were compared to examine SICI in the presence of SICI and SAI matched for amplitude and intensity, respectively.
adjusted to produce 1-mV MEPs in the presence of MNS$_{23}$. Conditions A–C gave SICI (B/A) and SAI (C/A) for a 1-mV test MEP. Similarly, SICI (E/D) and SAI (F/D) with an adjusted TS intensity (TS1mV$_{MNS23}$) were tested in conditions D–G. Condition G assessed the interactions between SAI and SICI. The experiment was designed to compare SICI in the presence of SAI (G/F) to SICI matched for test MEP amplitude (B/A) or TS intensity (E/D). We also compared SAI in the presence of SICI (G/E) to SAI alone with TS intensity of 1 mV (not matched for MEP amplitude) (C/A) and matched for TS intensity (F/D).

Experiments 3–6: Interactions Between SAI and SICI Under Different Experimental Conditions

In experiments 3–6, we tested how the interactions between SAI and SICI are affected by different CS intensities and ISIs (2 or 3 ms, CS$_2$ or CS$_3$) for SICI and different ISIs for SAI and the effects of voluntary contraction. Active motor threshold (AMT) was defined as the minimum stimulator output that induced MEPs of >200 μV in at least 5 of 10 consecutive trials when FDI muscle contracted at 20% maximum voluntary contraction (MVC). MNS preceded the TS by N$_20$ + 3 ms (SAI$_{23}$) or 25 ms (SAI$_{25}$).

Experiment 3: effects of different conditioning stimulus intensities on SAI-SICI interactions. We studied the effects of four different CS intensities (60%, 70%, 80%, 90% AMT) on SAI-SICI interactions. The conditions were identical to those in experiment 2 (Table 1) except that the intensities of CS to generate SICI were 60–90% of AMT. Since SICI may be contaminated with short-interval intracortical facilitation (SICF) (Peurala et al. 2008), condition H consisting of TS1mV$_{MNS23}$ followed by S$_2$, 2 ms later at the identical intensity (0.6–0.9 times AMT) used for eliciting SICI, was added. SICF was calculated as (H/ID). Condition G assessed the interactions between SAI and SICI. We tested the four CS intensities in four separate runs.

Experiment 4: effects of SICI at 3-ms ISI on SAI-SICI interactions. Since SICI and SICF change with ISI, we studied the effect of SICI elicited at 3-ms ISI on SAI-SICI interactions. The conditions were identical to those in experiment 3 (Table 1) except that SICI for SICI was delivered with 3-ms ISI and CS intensities were 70% or 90% of AMT.

Experiment 5: effects of SAI at 25 ms on SAI-SICI interactions. We studied the effects of SAI elicited by MNS at 25 ms before TMS (SAI$_{25}$) and SICI elicited at 2- or 3-ms ISI on SAI-SICI interactions. The ISI of 25 ms was chosen because it is commonly used in studies of PAS to induce plasticity in motor cortex (Elahi et al. 2012; Stefan et al. 2000, 2002). The conditions were the same as in experiment 3 except that MNS was given at 25 ms prior to TMS. We tested two CS intensities (0.7 and 0.9 AMT) with ISIs (2 and 3 ms) for SICI in four separate runs.

Experiment 6: effects of voluntary contraction on SAI-SICI interactions. The conditions were identical to experiment 4 except that the subjects voluntarily contracted the FDI muscle at 20% of MVC. We tested two CS intensities (0.7 and 0.9 AMT) with ISIs of 2 and 3 ms for SICI in four separate runs.

Data Analysis

MEP amplitudes were measured peak to peak. SICI and SAI were expressed as the ratio of the conditioned (with preceding CS) to the unconditioned (TS alone) MEP amplitudes as outlined above. Depending on the ISI, SICI$_1$ and SICI$_2$ were defined for SICI of 2 and 3 ms, respectively. A ratio > 1 indicates facilitation, and a ratio < 1 indicates inhibition. Values are expressed as means ± SD. For experiment 1, the effects of different test MEP amplitudes on SICI and SAI were tested by repeated-measures analysis of variance (ANOVA) and Fisher’s protected least significance difference (PLSD) post hoc test. StatView software was used for statistical analysis. For experiments 2–6, the effects of SAI on SICI were determined by repeated-measures ANOVA by comparing SICI for TS1mV (B/A), SICI for TS1mV$_{MNS23}$ (E/D), and SICI in the presence of SAI (G/F) (termed “SICI condition”) as the repeated measures. Similarly, the effects of SICI on SAI were examined by repeated-measures ANOVA with test conditions of SAI for TS1mV (C/A), SAI for TS1mV$_{MNS23}$ (G/D), and SAI in the presence of SICI (G/E) as repeated measures (termed “SAI condition”). Post hoc Fisher’s PLSD test was used to examine which condition was different from others if ANOVA showed a significant main effect. Correlation analyses were used to determine whether the triple-pulse-induced changes in SAI and SICI were related to SAI, SICI, or both. Pearson’s correlation coefficient was used to examine how “SICI in the presence of SAI (G/E)” or “SAI in the presence of SICI (G/E)” is related to the strength of SICI (E/D) and SAI (F/D). Bartlett’s test was used to test for sphericity. The threshold for significance was set at $P < 0.05$.

RESULTS

The latencies of the N$_{20}$ component of the median nerve somatosensory evoked potential were 19.4 ± 1.1 ms (n = 20), RMT was 50.7 ± 4.6% and AMT was 42.2 ± 3.4% of the stimulator output. Bartlett’s test for sphericity was not significant for the data presented below.

Experiment 1: Effects of Different Test Stimulus Intensities on SICI and SAI Interactions

The findings for the effects of different test stimulus intensity on SAI were published in our earlier report (Udupa et al. 2009). The TS intensities used were 60.1 ± 8.3% of stimulator output for TS0.2mV, 67.5 ± 11.4% for the TS1mV condition, and 79.6 ± 13.2% for TS2mV. The amplitudes for test MEP alone were 0.21 ± 0.05 mV for TS0.2mV, 1.11 ± 0.35 mV for TS1mV, and 2.24 ± 0.77 mV for TS2mV. The results are shown in Fig. 1A. SICI showed little inhibition at TS0.2mV, and it increased with TS intensity. Repeated-measures ANOVA showed no significant effect of the type of inhibition (SAI and SICI) or TS intensities, but there was a significant interaction ($F = 11.96; P < 0.001$) between type of inhibition and TS intensity. To explore the significant interaction effect, we performed separate ANOVA for SICI and SAI. ANOVA for SICI showed a significant effect of TS intensity ($F = 5.62; P = 0.02$). Post hoc testing showed less SICI at TS0.2mV compared with TS1mV ($P = 0.02$) and with TS2mV ($P = 0.009$). On the other hand, the effect of test MEP amplitude on SAI was not significant, although there was a trend for less SAI with higher test MEP amplitude. The different responses for SICI and SAI to the increasing TS intensities suggest that different neuronal populations are involved in these two circuits.

Experiment 2: Effect of SAI on SICI (SAI$_{25}$, CS 0.8 RMT, rest)

The data from one subject were excluded from the analysis as the MEP amplitude in the presence of MNS$_{23}$ (condition F, Table 1) could not be matched with that of TS1mV alone (condition A). TS intensities used were 67.9 ± 9.9% of stimulator output for eliciting target MEPs of 1 mV (condition A) and 75.6 ± 12.0% for MEPs of 1mV$_{MNS23}$ (condition D). RMT was 50.7 ± 4.6% (80% RMT = 40.6 ± 3.7% = ~95% of AMT used in experiments 3–6). The MEP amplitudes were 1.05 ± 0.46 mV for the 1-mV test MEP (condition A), 1.86 ± 0.65 mV for 1mV$_{MNS23}$ (condition D), and 1.24 ± 0.53 mV for
of 0.8 resting motor threshold (RMT) and SICI2 (Intensities on SICI and SAI Interactions experiment 3: Effects of Different Conditioning Stimulus additive. Thus the effects of SAI and SICI appear to be C 0.38; Fig. 1. Figure 1, F in the presence of SAI (SICI conditions, although SICI appears to be slightly reduced subject are shown in Fig. 2. SAI had no significant effect on the amplitudes for the 1-mV test MEP (MEP) amplitude. Values y-axis shows the ratio of the conditioned [conditioning stimulus (CS) followed by TS] to the unconditioned (TS alone) motor evoked potential (MEP) amplitude. Values < 1 represent inhibition. Error bars represent SE. Target MEP amplitudes of 0.2 mV, 1 mV, and 2 mV are shown. Significant differences as shown by repeated-measures ANOVA and post hoc testing: *P < 0.05, **P < 0.01. B: interactions between SICI and SAI at CS intensity of 0.8 resting motor threshold (RMT) and SICI2 (experiment 2). y-Axis shows SICI as ratio of the conditioned vs. the unconditioned MEP. Ratios < 1 represent inhibition; ratios > 1 represent facilitation. Error bars represent SE. SICI in the presence of SAI was compared with SICI alone matched for TS amplitude (TS1mV) and TS intensity (TS1mVMNS23). SICI was not significantly different in the presence of SAI. C: interactions between SAI and SICI at CS intensity of 0.8 RMT and SICI2 (experiment 2). SAI in the presence of SICI was compared with SAI alone matched for TS amplitude (TS1mV) and TS intensity (TS1mVMNS23). SAI was not significantly different in the presence of SICI.

the MNS23-1mVMNS23 test pulse combination (condition F). Thus the amplitudes for the 1-mV test MEP (condition A) and the MNS23-1mVMNS23 test MEP (condition F) were matched. Figure 1, B and C, show the group results, and results from one subject are shown in Fig. 2. SAI had no significant effect on the SICI conditions, although SICI appears to be slightly reduced in the presence of SAI (F = 1.89; P = 0.18; Fig. 1B). There was no significant effect of SAI conditions (F = 1.04; P = 0.38; Fig. 1C). Thus the effects of SAI and SICI appear to be additive.

Experiment 3: Effects of Different Conditioning Stimulus Intensities on SICI and SAI Interactions

The TS intensities used were 58.6 ± 4.7% of stimulator output for the TS1mV condition and 65.1 ± 4.5% for TS1mVMNS. The amplitudes for TS alone were 0.99 ± 0.26 mV for TS1mV (condition A), 3.31 ± 1.31 mV for TS1mVMNS (condition D), and 1.11 ± 0.18 mV for TS1mVMNS with MNS (condition F). Thus conditions A and F were matched for MEP amplitude. The effects of different CS intensities (60–90% AMT) on SAI-SICI interactions are shown in Fig. 3A. Repeated-measures ANOVA showed significant main effects of CS intensity (F = 16.66; P < 0.001) and “SICI conditions” (F = 5.29; P = 0.02) on SICI. Post hoc tests showed significantly

Fig. 1. A: effects of different test stimulus (TS) intensities on short-interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI) in experiment 1. y-Axis shows the ratio of the conditioned [conditioning stimulus (CS) followed by TS] to the unconditioned (TS alone) motor evoked potential (MEP) amplitude. Values < 1 represent inhibition. Error bars represent SE. Target MEP amplitudes of 0.2 mV, 1 mV, and 2 mV are shown. Significant differences as shown by repeated-measures ANOVA and post hoc testing: *P < 0.05, **P < 0.01. B: interactions between SICI and SAI at CS intensity of 0.8 resting motor threshold (RMT) and SICI2 (experiment 2). y-Axis shows SICI as ratio of the conditioned vs. the unconditioned MEP. Ratios < 1 represent inhibition; ratios > 1 represent facilitation. Error bars represent SE. SICI in the presence of SAI was compared with SICI alone matched for TS amplitude (TS1mV) and TS intensity (TS1mVMNS23). SICI was not significantly different in the presence of SAI. C: interactions between SAI and SICI at CS intensity of 0.8 RMT and SICI2 (experiment 2). SAI in the presence of SICI was compared with SAI alone matched for TS amplitude (TS1mV) and TS intensity (TS1mVMNS23). SAI was not significantly different in the presence of SICI.

Fig. 2. Effects of SAI on SICI in a representative subject. Each trace represents averaged MEPs from 10 trials. A: TS alone. TS was set to produce MEP of −1 mV (condition A in Table 1). B: TS1mVMNS23 alone. TS was adjusted to produce test MEP of 1 mV in the presence of median nerve stimulation (MNS23) preceding the TS by −23 ms (condition D). C: SAI induced by MNS23 preceding the TS 1mVMNS23 by −23 ms (condition F). The MEP amplitude matched was similar to the MEP amplitude in condition A. D: SICI elicited by a subthreshold conditioning stimulus (CS2) that preceded the TS1mVMNS23 by 2 ms (condition E). E: combined SAI and SICI (MNS23, CS2-TS1mVMNS23 combination, condition G). The inhibition is greater compared with C and D, demonstrating that there is an additive effect of the 2 inhibitory pulses.
A short afferent inhibition and short-interval intracortical inhibition

Fig. 3. Effects of different CS intensities on SICI, SAI, and short-interval intracortical facilitation (SICF). A: interactions between SICI and SAI and SICI at different CS intensities (0.6–0.9 AMT) for SICI. y-Axis shows SICI as the ratio of the conditioned vs. the unconditioned MEP. Ratios < 1 represent inhibition; ratios > 1 represent facilitation. Error bars represent SE. SICI in the presence of SAI was compared with the SICI alone matched for test MEP amplitude (TS1mV) and TS intensity (TS1mV MNS23). SICI was significantly decreased in the presence of SAI for all CS intensities for SICI. B: interactions between SICI and SAI at different CS intensities (0.6–0.9 AMT) for SAI. y-Axis shows SAI as the ratio of the conditioned vs. the unconditioned MEP. Ratios < 1 represent inhibition. Error bars represent SE. SAI in the presence of SICI was compared with SAI alone matched for test MEP amplitude (TS1mV) and TS intensity (TS1mV MNS23). SAI was reduced in the presence of SICI for all CS intensities studied. C: effect of different CS intensities (0.6–0.9 AMT) on SICF. y-Axis shows SICF as the ratio of the conditioned vs. the unconditioned MEP (H/D). Ratios < 1 represent inhibition; ratios > 1 represent facilitation. Error bars represent SE. Facilitation was not observed for all the CS intensities studied.

less inhibition (higher values) for SICI in the presence of SAI to both SICI matched for amplitude and intensity (P < 0.01). The CS intensity × “SICI condition” interaction (F = 0.22, P = 0.97) was not significant.

We also compared the effects of different SICI-CS intensities on SAI and SAI in the presence of SICI. Repeated-measures ANOVA showed significant main effects of SAI conditions (F = 3.86; P = 0.04). Post hoc testing showed significantly less SAI in the presence of SICI to the SAI matched for TS intensity (P = 0.01) (Fig. 3B) but not to SAI matched (see below) for MEP amplitude and no significant effects of CS intensity or CS intensity × “SAI conditions” interaction. It should be noted that the MEP amplitudes of condition E (SICI with test intensity TS1mV MNS23) were 2.9 ± 1.7 mV (0.6 AMT), 2.2 ± 1.5 mV (0.7 AMT), 0.95 ± 0.5 mV (0.8 AMT), and 0.8 ± 0.6 mV (0.9 AMT). Thus the analysis of SAI in the presence of SICI was matched for MEP amplitudes at CS of 0.8 and 0.9 AMT, which had MEP amplitudes of ~1 mV, but not at the lower CS intensities. However, when we compared SAI in the presence of SICI (G/E) and SAI matched for intensity (I/D) and amplitude (C/A) for these two intensities (0.8 and 0.9 AMT), there was still only a significant main effect of SAI conditions (F = 3.58, P = 0.05). It is interesting to note that in Fig. 3B only the “presence of SICI” bar contains SICI (the other 2 bars are SAI only and are identical conditions across different CS intensities for SICI). Increasing SICI leads to greater interaction between SICI and SAI, further suggesting that there is a “dose-dependent” effect of SICI on this interaction. However, experiment 2, which used higher SICI, did not show any significant interaction (Fig. 1C) but the MEP amplitude of condition E (SICI with test intensity TS1mV MNS23) was 0.63 ± 0.54 mV and was not matched to 1 mV.

For SICF, there was no significant difference between the MEP amplitudes for conditions D (test alone) and H (paired pulse to activate SICF) for the CS intensities studied (the ratio H/D was ~1, showing no facilitation; Fig. 3C), indicating that no SICF was elicited in our experimental protocol.

Experiment 4: Effects of ISI for SICI (SICI2 vs. SICI3) on SAI-SICI Interactions

We tested the SAI-SICI interactions at ISI of 3 ms for SICI and compared the results to experiment 3, which used 2-ms ISI for SICI. We selected 3-ms ISI because it may be contaminated by SICF (Peurala et al. 2008). The amplitudes for test MEP alone were 1.10 ± 0.30 mV for TS1mV (condition A), 2.73 ± 0.9 mV for TS1mV MNS (condition D), and 1.19 ± 0.21 mV for TS1mV MNS with MNS (condition F). Thus conditions A and F were matched for MEP amplitude. Repeated-measures ANOVA showed significant main effects of CS intensity (0.7 and 0.9 AMT; F = 28.5, P < 0.001; stronger SICI for CS of 0.9 AMT) and SICI conditions (F = 11.89; P < 0.001; post hoc tests showed that SICI in the presence of SAI was significantly less than SICI matched for amplitude and intensity, P < 0.001) and a trend for ISI (2 and 3 ms; F = 4.59, P = 0.06, stronger SICI2) on SICI (Fig. 4A). The ISI × SICI condition interaction was significant (F = 6.13; P < 0.01). Figure 4A shows that the interaction was due to much more prominent reduction of SICI and turning to facilitation in the presence of SAI at SICI3 compared with SICI2. The other interactions between ISI, CS intensity, or SICI conditions were not significant.

For the effects of SICI on SAI (Fig. 5A), the main effect of SAI conditions was significant (F = 11.58; P < 0.001). Post hoc testing for SAI conditions showed that SAI in the presence of SICI was significantly less than SAI matched for amplitude (P < 0.001) and intensity (P < 0.001). The effect of ISI (F = 14.67, P = 0.004) and the interaction between ISI and SAI conditions (F = 9.05; P < 0.002) were significant, indicating more inhibition of SAI in the presence of SICI compared with SICI2. There were no main effects for SICI-CS intensities (0.7 and 0.9 AMT) and no significant interactions between intensities and either ISI or SAI conditions (Fig. 5, A and B).
ANOVA (SICI CS intensities: 0.7 and 0.9; SICI conditions and MNS latencies as factors) and found main effects of CS intensity \( (F = 18.71, P = 0.002); \) less SICI with 0.7 AMT) and SICI conditions \( (F = 4.65, P = 0.02); \) SICI in the presence of SAI is less than SICI matched for amplitude and intensity) but no effects of MNS latency and no interaction among these factors.

Similarly, for SICI \(_3\) (Fig. 4, A and B, right), three-way ANOVA showed main effect of CS intensity \( (F = 19.54, P = 0.002); \) less SICI with 0.7 AMT) and SICI conditions \( (F = 19.73, P < 0.001); \) SICI in the presence of SAI is less than SICI matched for amplitude and intensity) and a trend for interaction between SAI latency and SICI condition \( (F = 3.36, P = 0.06); \) greater disinhibition of SICI in the presence of SAI\(_{23}\) than SAI\(_{25}\) but no main effect of MNS latency and no interaction among other factors.

\begin{itemize}
  \item \textbf{Experiment 6: Effects of Voluntary Contraction on SAI-SICI Interactions}
  \item Results are shown in Fig. 6A for SICI\(_1\) and in Fig. 6B for SICI\(_3\). Voluntary contraction reduced SICI \( (0.99 \pm 0.58, t = 4.4, P = 0.002)\) for SICI\(_2\), 0.7 AMT; \( 1.51 \pm 0.81, t = 2.6, P = \)...
\end{itemize}
Voluntary contraction reduced SAI in experiment 6 (0.94 ± 0.072; t = 3.13; P = 0.01) compared with the resting state (0.48 ± 0.36). We examined the effects of activity (resting and voluntary contractions), SICI-CS intensities (0.7 and 0.9 AMT), and SICI- ISI (2 and 3 ms) on SAI in the presence of SAI (SAI conditions). Four-way repeated-measures ANOVA showed significant main effects of SICI-ISI (F = 19.6; P = 0.002) and SAI condition (F = 19.23; P = 0.0001) but no significant main effects of activity and SICI-CS intensity. There was significant interaction for ISI × SAI conditions (F = 3.74; P = 0.03, greater SAI-SICI interactions at 3-ms CS- ISI) but no other interaction effect (Fig. 7).

Correlations Between Interactions of SICI and SAI and Magnitudes of SICI and SAI

We correlated the combined inhibitory effects of SICI and SAI to SICI and SAI alone to examine the factors that affect the interactions between these two circuits. SICI in the presence of SAI correlated with SICI (conditions E/ D) at 0.9 AMT CS intensity (Fig. 8A; R = 0.67, P = 0.03), whereas SAI in the presence of SICI did not correlate with SAI (conditions F/ D) (Fig. 8B; R = 0.18, P = 0.61). We also compared the MEP amplitude when triple pulses were given (MNS-CSs-TS, condition G) to the paired-pulse conditions (MNS-TS, condition F and CS-TS, condition E) to study the interactions of these two

The state of muscle activity (resting vs. voluntary contraction) was significantly different in the presence of SAI compared with SICI 1 mV in the active than in the rest condition), activity and ISI (F = 20.71; P = 0.001, greater reduction of SICI from rest to active with CS than CSs), activity and CS intensity (F = 14.16; P < 0.005, greater reduction in SICI from rest to active for higher (0.9 AMT) than lower (0.7 AMT) intensity), and activity × ISI × SICI conditions (F = 4.10; P = 0.034).

To further understand the significant interactions, the two different ISIs for SICI were analyzed separately. For SICI3 (Fig. 6A), there were significant main effects of muscle activity (F = 37.60, P = 0.0002; reduced SICI in active condition) and SICI conditions (F = 7.05; P = 0.006) on the extent of SICI but no significant main effects of CS intensity. There was significant muscle activity × CS intensity interaction (F = 28.34, P = 0.0005), and Fig. 6A shows that muscle activity produced greater reduction in SICI for CS of 0.9 AMT compared with 0.7 AMT. The muscle activity × SICI condition interaction (F = 6.54; P = 0.007) was also significant, and this appears to be due to relatively greater reduction in SICI from the rest state to the active state in the TS1mV condition and smaller difference in SICI in the presence of SAI compared with SICI 1 mV in the active than the rest condition. For SICI3 (Fig. 6B), there was no significant main effect of muscle activity but significant main effects of CS intensity (F = 7.06; P = 0.03; stronger SICI with 0.9 AMT) and SICI conditions (F = 14.75; P = 0.0002). Also, there was significant interaction between SICI and activity intensity (F = 18.97; P = 0.002), with reduction in SICI following voluntary activity being more prominent for 0.9 AMT than for 0.7 AMT. There were no significant interactions between muscle activity and SICI conditions or between intensity and SICI conditions.
circuitry. The MEP amplitude when both inhibitory circuits were activated (MNS-CS₂-TS) correlated with the MEP of SICI (CS₂-TS) (Fig. 8C; \( R = 0.66, P = 0.04 \)) but not that of SAI (MNS-TS) (Fig. 8D; \( R = 0.32, P = 0.37 \)). These significant correlations of SICI in the presence of SAI with SICI suggest that SICI likely inhibits rather than SAI inhibiting SICI.

We correlated the changes from SAI-SICI interaction during voluntary contraction to the individual intracortical circuit (SAI and SICI alone). SICI in the presence of SAI significantly correlated with SICI at intensities of 0.9 AMT (\( R = 0.63; P = 0.05 \); Fig. 8E), whereas SAI in the presence of SICI did not correlate with SAI (\( R = 0.11; P = 0.77 \); Fig. 8F), suggesting that effects of SICI predominated when SICI and SAI were applied together during voluntary contraction.

**DISCUSSION**

We examined the interactions between SAI and SICI under different conditions. Afferent stimulation that produced SAI had inhibitory interaction with SICI at different CS intensities of SICI in both rest and active conditions at SAI₂₃ or SAI₂₅. This interaction occurred at weak SICI when there was no MEP inhibition (e.g., CS of 0.6 AMT) and SICI in the presence of SAI became facilitatory. The inhibitory effect of SICI on MEP is different from that of SAI. SICI correlates with SICI in the presence of SAI, but SAI does not correlate with SICI in the presence of SICI, suggesting that the effects of SICI are dominant over those of SAI in determining the outcome of SAI-SICI interaction. Interaction between SAI and SICI was greater for SICI₂ than for SICI₁, even though the inhibitory strength of SICI₂ is stronger than that of SICI₃.

**Importance of SICI-SAI Interaction**

The interactions between SAI and SICI have implications for other protocols such as PAS that incorporate repeated pairing of MNS and TMS around the range of ISI used for SAI (Stefan et al. 2000). However, the mechanisms of SAI and PAS are different, as SAI is based on single pairing of MNS and TMS whereas PAS involves repeated pairings of these two stimuli. A recent study found involvement of cerebellar neuronal circuits in longer-latency PAS (PAS₂₅) and but not in shorter-latency PAS₂₁.₅ (Hamada et al. 2012). Furthermore, SAI was found to be abnormal in PD (Sailer et al. 2003) and AD (Di Lazzaro et al. 2002) but is normal in frontotemporal dementia (Di Lazzaro et al. 2006) and may be used to predict treatment response in AD (Di Lazzaro et al. 2005a) and prognosis in stroke patients (Di Lazzaro et al. 2012). SAI was reduced by intravenous administration of scopolamine, a cholinergic muscarinic (M1) receptor antagonist (Di Lazzaro et al. 2000), but is also decreased by certain benzodiazepines that potentiate GABA transmission (Di Lazzaro et al. 2007). Dopaminergic drugs decrease SAI (Sailer et al. 2003) in PD (Sailer et al. 2007). On the basis of these findings, it was suggested that SAI may reflect the functions of central cholinergic circuits. Recordings of corticospinal waves in the cervical spinal cord showed that SAI is due to cortical inhibition (Tokimura et al. 2000). It has been postulated that SAI is mediated by afferent inputs from thalamus directly to M1 or via a short relay through the primary sensory cortex. Therefore, inhibitory or facilitatory circuits in the M1 may affect SAI. Hence, it is important to understand the effects of SAI on SICI, which is considered one of the main intracortical inhibitory circuits.

**Different Neuronal Circuits Mediate SICI and SAI**

**Experiment 1** showed that SICI increased with higher test MEP amplitude while SAI showed no significant change. The findings for SICI are in agreement with previous studies (Sailer et al. 2002; Sanger et al. 2001), although SAI has not been studied in this manner. Since changes in test stimulus intensities had different effects for the different types of cortical inhibition and facilitation, different sets of neuronal circuits likely mediate SICI and SAI (Chen 2004). Furthermore, SAI was influenced by benzodiazepines that enhance GABA_A-mediated inhibition. Lorazepam markedly reduced SAI, whereas diazepam had no significant effect. In contrast, both drugs increase SICI, suggesting that diazepam and lorazepam may have similar affinity to the GABA receptor subtypes that mediate SICI, while they show different affinity to those involved in SAI (Di Lazzaro et al. 2005b, 2007). Inhibition of SAI by lorazepam could be explained by GABA_A receptor-mediated reduction of acetylcholine release (Di Lazzaro et al. 2005b). Pharmacological studies showed that SICI is likely mediated by GABA_A receptors (Di Lazzaro et al. 2000; Muller-Dahlhaus et al. 2008; Werhahn et al. 1994; Ziemann et al. 1996). Normal SAI in PD is decreased by dopaminergic drugs (Sailer et al. 2003), whereas SICI is reduced in PD and is partially normalized by dopaminergic medications (Chu et al. 2009; Ni et al. 2013; Ridding et al. 1995a; Ridding and Rothwell 1995; Sailer et al. 2007). Taken together, our findings and those of previous studies suggest that SAI and SICI are mediated by different neuronal circuits involving different neurotransmitters with possible interaction between these circuits and neurotransmitter systems. Study of the interactions between SAI and SICI circuits improves the understanding of...
motor cortical networks and potentially provides further cues on the pathophysiology of neurological and psychiatric disorders.

**Effects of SAI on SICI at Different CS Intensities**

Since we found no significant interaction between SAI and SICI at 80% RMT (approx. 95% AMT) (*experiment 2*), we extended our study to different CS intensities (0.6–0.9 AMT) for SICI. The strength of SICI varied from almost no SICI at 0.6 AMT (Fig. 3A) to maximum SICI at ~0.9 AMT. We found inhibitory interactions between SAI and SICI for CS intensities from 0.6 to 0.9 AMT. An important observation is that at lower CS intensities of 0.6 and 0.7 AMT that produced SICI, SAI and SICI still showed inhibitory interactions (Fig. 3A and Fig. 8A).

This effect cannot be explained by saturation of inhibition because of weak SICI (only ~10% inhibition at 0.6 AMT; Fig. 8A).
3A), and interaction resulted in facilitatory response (ratio > 1). Furthermore, this effect is similar to the interaction between LICI and SICI in which weak LICI that did not produce MEP inhibition still disinhibits SICI (Sanger et al. 2001). Thus the SICI circuits responsible for MEP inhibition are likely distinct from those mediating disinhibition of SAI. The reason for this difference is not known, but one possible explanation is that lower CS intensities (such as 0.6 AMT) are subthreshold to cortical inhibitory neurons but activate the more superficial (easily excitable segment) inhibitory dendritic branch of these neurons, inhibiting neurons that mediate SAI, thus ultimately producing disinhibition. These GABA$_A$-mediated interneuron interactions could be explained by the axo-axonic interactions of the circuits involved (Ren et al. 2007).

There are several possible reasons why we found significant interaction between SAI and SICI in experiments 3–6 but not in experiment 2, which showed a nonsignificant trend (Fig. 1, B and C). The inhibitory interaction between SAI and SICI occurs at lower CS intensities for SICI, whereas the inhibitory interaction was not present at the CS intensity used in experiment 2 (0.8 RMT, equivalent to $\sim$0.95 AMT). Higher CS intensities might activate other circuits, such as SICF. Since increasing CS intensities produced a U-shaped curve on the MEP amplitude ratio (Chen et al. 1998; Peurala et al. 2008), SICI produced by 0.8 RMT ($\sim$0.95 AMT, 60% inhibition; Fig. 1B) is weaker than 0.9 AMT (70% inhibition; Fig. 3A). This in turn might have reduced interaction with SAI. Moreover, different sets of subjects were tested in experiments 2 and 3, and different subjects may show considerable differences in the strength of cortical circuits tested (Boroojerdi et al. 2000).

For the effects of SAI in the presence of SICI (Fig. 3B), SAI-SICI interaction was prominent at higher intensities of SICI (0.8 and 0.9). Thus increasing SICI resulted in increased SICI-SAI interaction, indicating the dose-dependence effect of SICI.

**Effect of Different ISIs for SICI on SICI-SAI Interactions**

We found a trend for stronger SICI$_2$ than SICI$_3$, consistent with earlier reports (Kujirai et al. 1993; Vucic et al. 2009). The SICI$_3$ used by Stefan et al. (2002) may be contaminated by SICF, whereas SICI$_2$ is less likely to be affected (Peurala et al. 2008). Hence, we studied the influence of both ISIs on SAI-SICI interactions and also tested SICF. Since we found no SICF at the CS intensities and ISI studied, SICF is unlikely to explain our results. Another study (Alle et al. 2009) showed inhibitory SAI-SICI interactions for different CS-SICI ISIs (1, 1.5, 2.1, 2.7, and 3 ms) with no significant difference between them, but it was performed in the active condition and the resting state was not studied. We found that CS-ISI influences SAI-SICI interactions at rest as demonstrated by a significant ISI $\times$ SICI condition interaction (Fig. 4 and Fig. 5) with SICI$_3$ producing greater inhibitory interaction with SAI than SICI$_2$. This cannot be explained by different strengths of inhibition for SICI$_2$ and SICI$_3$, as SICI$_2$ was stronger at 0.7 AMT while SICI$_3$ was stronger at 0.9 AMT but at both CS intensities the SAI-SICI interaction was greater for SICI$_2$. There may be subtle differences in cortical circuits activated by SICI$_2$ and SICI$_3$.

**Effect of SAI Latency on SAI-SICI Interactions**

We found that afferent inhibition produced by SAI$_{23}$ is stronger than SAI$_{25}$, consistent with previous studies (Tomikura et al. 2000). There were interactions between SICI and SAI at both latencies (SAI$_{23}$ and SAI$_{25}$), and our results for SAI$_{25}$ are similar to those of a previous study (Stefan et al. 2002) that investigated the effects of SAI$_{25}$ with MNS at three times the sensory threshold on the SICI$_3$ at a CS intensity of 70% RMT. It was observed that SAI$_{25}$ reduced SICI$_3$, measured in the APB muscle (median innervated). We observed a trend for interaction between SAI latency and SICI conditions (at CS$_3$), suggesting that the interaction between SICI and SAI was greater at SAI$_{23}$ than at SAI$_{25}$. This may be explained by the finding that there is more SAI to inhibit in SAI$_{23}$ than in SAI$_{25}$. Since SAI$_{25}$ is known to involve cerebellar circuits with repeated pairing through PAS25 (Hamada et al. 2012), the neuronal circuits mediating these two latencies of SAI are likely different. Further studies with different latencies of MNS and the neuronal pathways involved may provide further insights on the effects of afferent inhibition latencies.

**Effects of Voluntary Contraction on SAI-SICI Interactions**

Voluntary contraction reduced both SICI and SAI. The reduction of SICI with voluntary contraction is consistent with previous reports (Coxon et al. 2006; Ni et al. 2007; Ridding et al. 1995b) and is partially due to the activation of SICF (Ortu et al. 2008). However, our finding of decreased SAI with voluntary activity has not been reported.

Previous studies (Alle et al. 2009; Stefan et al. 2002) did not compare SICI-SAI interaction between the rest and active states. Voluntary contraction reduced the inhibitory SAI-SICI interaction as demonstrated by a significant interaction effect of voluntary contraction and SICI conditions in experiment 6. This may be due to reduced SAI and SICI with voluntary contraction, leading to reduction in their interaction as there was less SAI or SICI to inhibit. Studies have found graded reduction in the inhibitory effects of different levels of voluntary contraction on SICI to maintain the precision level (Kouchtir-Devanne et al. 2012). Thus reduction of inhibitory interaction during voluntary contraction in our study indicates the role of voluntary activity on interactions of inhibitory circuits to achieve better precision of the desired task. Furthermore, it would be interesting to study the contribution at different levels of voluntary contraction (10–100%) on the SAI-SICI interactions. Interestingly, the interaction between SICI conditions and activity was not significant for SICI$_3$, whereas it was significant for SICI$_1$, indicating that the voluntary activity had greater effect on SAI-SICI interaction for SICI$_1$ than SICI$_3$, which explains the significant three-way activity $\times$ ISI $\times$ SICI condition interaction. This may be because there was greater reduction of SICI$_2$ with muscle contraction than of SICI$_1$, leading to better preserved inhibitory interaction between SICI and SAI with voluntary contraction for SICI$_1$. Thus we conclude that voluntary activity decreases both SAI and SICI circuits and also reduces their inhibitory interaction, but more so for SICI$_2$ than SICI$_3$.

**SICI Inhibiting SAI**

In light of the significant correlations of SICI in the presence of SAI to SICI and not the other way round, it is likely that the
Short-interval intracortical inhibition is decreased but the mechanism of SICI-mediated MEP inhibition is likely to act in a complex manner. SICI and SAI have inhibitory latency, and activity status of the target muscle all influence the inhibition of SICI by SAI. This suggests that inhibitory interaction between SICI and SAI is predominantly due to SICI inhibiting SAI. Also, the apparent facilitation for SICI in the presence of SAI when there was little or no SICI (rest 0.6 AMT and SICI during voluntary activity) can be explained by inhibition of SAI by SICI but not by SAI inhibiting SICI, as there is no SICI to inhibit. However, we also observed SAI turning into facilitation in the presence of SICI3 (Fig. 5 and Fig. 7), suggesting that there is also facilitation of SICI by SAI.

Conclusions

We found that CS intensity for SICI, ISI for SICI, MNS latency, and activity status of the target muscle all influence the interaction between SICI and SAI and that these factors interact in a complex manner. SICI and SAI have inhibitory interactions. This is predominantly due to SICI inhibiting SAI, but the mechanism of SICI-mediated MEP inhibition is likely different from that of SAI inhibition. SAI likely also inhibits SICI. The interaction increases with the strength of SICI and is more prominent with SICI3 than with SICI2. It is decreased with voluntary contraction, and this decrease is more pronounced with SICI2 than with SICI3. Studying such interactions in neurological disorders such as AD and PD, which are known to involve one or both of these circuits, may provide further insights into the pathophysiology of these disorders. This may be particularly relevant in PD, since presynaptic inhibition (the interaction between LICI and SICI) is impaired in PD (Chu et al. 2009).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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