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Influence of Waveform and Current Direction on Short-Interval Intracortical Facilitation: A Paired-Pulse TMS Study

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) of the human primary motor hand area (M1-HAND) can produce multiple descending volleys in fast-conducting corticospinal neurons, especially so-called indirect waves (I-waves) resulting from trans-synaptic excitation. Facilitatory interaction between these I-waves can be studied non-invasively using a paired-pulse paradigm referred to as short-interval intracortical facilitation (SICF).
Objective/hypothesis: We examined whether SICF depends on waveform and current direction of the TMS pulses.
Methods: In young healthy volunteers, we applied single- and paired-pulse TMS to M1-HAND. We probed SICF by pairs of monophasic or half-sine pulses at suprathreshold stimulation intensity and inter-stimulus intervals (ISIs) between 1.0 and 5.0 ms. For monophasic paired-pulse stimulation, both pulses had either a posterior–anterior (PA) or anterior–posterior (AP) current direction (AP–AP or PA–PA), whereas current direction was reversed between first and second pulse for half-sine paired-pulse stimulation (PA–AP and AP–PA).
Results: Monophasic AP–AP stimulation resulted in stronger early SICF at 1.4 ms relative to late SICF at 2.8 and 4.4 ms, whereas monophasic PA–PA stimulation produced SICF of comparable size at all three peaks. With half-sine stimulation the third SICF peak was reduced for PA–AP current orientation compared with AP–PA.
Conclusion: SICF elicited using monophasic as well as half-sine pulses is affected by current direction at clearly suprathreshold intensities. The impact of current orientation is stronger for monophasic compared with half-sine pulses. The direction-specific effect of paired-pulse TMS on the strength of early versus late SICF shows that different cortical circuits mediate early and late SICF.

Introduction

Transcranial magnetic stimulation (TMS) is a widely used tool to probe motor cortex excitability [1]. In humans, a single monophasic TMS pulse applied to the primary motor hand area (M1-HAND) can produce multiple descending volleys in the fast-conducting corticospinal neurons, which may be recorded using invasive epidural recordings in non-human primates and humans [2–4]. These volleys have different latencies, originate either from axonal or trans-synaptic excitation of fast-conducting corticospinal neurons, and have consequently been termed direct wave (D-wave) and indirect waves (I-waves), respectively [2]. There is always only

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a single D-wave, which has the shortest latency. Following the D-wave, up to five I-waves—termed I_1, I_2, and so on—occur with a difference in latency between consecutive I-waves of approximately 1.5 ms [5,6]. I-waves are of intracortical origin and are caused by transcranial excitation of trans-synaptic inputs that project onto corticospinal output neurons [3].

If TMS induces a sagittally oriented tissue current, stimulation will primarily produce I-waves [7–10]. Changing current direction of the sagittally oriented TMS pulse influences the generation of I-waves. A monophasic TMS pulse inducing a posterior–anterior (PA) directed current in M1-HAND preferentially evokes early I-waves [9,11], whereas an anterior–posterior (AP) directed current preferentially evokes late I-waves [9,11].

Using a conditioning-test paradigm, paired-pulse TMS can be used to study inhibitory and facilitatory phenomena in human M1-HAND [12]. If two slightly suprathreshold monophasic stimuli with PA orientation are given at variable inter-stimulus intervals (ISIs) between 1.0 and 5.0 ms, paired stimulation facilitates the amplitude of motor evoked potentials (MEP) in the relaxed target muscle compared to MEPs evoked by a single pulse [13]. Paired-pulse facilitation consistently occurs at distinct ISIs of around 1.5, 3.0 and 4.5 ms with little inter-study variability, and this facilitatory phenomenon has been named "short-interval intracortical facilitation" (SICF) [13–18]. Because the intervals between peaks correspond to the latencies between consecutive I-waves, SICF likely reflects a facilitatory interaction of intracortical circuits producing I-waves in fast-conducting corticospinal neurons [19]. Spinal mechanisms can largely be ruled out because subthreshold stimuli also yield SICF [14]. Furthermore, SICF cannot be induced when using transcranial electric stimulation instead of TMS [13,14].

In single-pulse TMS, the pulse waveform and the direction—PA vs. AP—of the induced tissue current influence preferential generation of early or late I-waves [7,9,20–22]. For paired-pulse TMS, however, the impact of pulse waveform and current direction remains to be studied. The SICF protocol is ideally suited to address this issue because SICF is thought to reflect a facilitatory interaction among cortical circuits generating I-waves. Besides monophasic pulses, half-sine waves can be applied at short ISIs needed to probe SICF. Compared with monophasic pulses, the electrical field induced by half-sine waves is less asymmetric, which likely impacts on preferential activation of certain I-waves [21].

We investigated the effect of two different waveforms and of reversing current direction on SICF recorded with the conventional paired-pulse paradigm at suprathreshold intensities. We hypothesized that changing current direction from PA to AP for monophasic pulses has a strong impact on SICF depending on the preferential I-wave recruitment of this waveform. Furthermore, we tested if half-sine pulses can also induce facilitatory I-wave interaction and investigated the effect of oppositely oriented half-sine pulses on SICF.

Methods

Participants

Fourteen healthy volunteers (9 women, 5 men) aged 22–37 years (mean 25.3 ± 1.3 years) participated in the study. All participants gave written informed consent. The study was approved by the local Ethics Committee and carried out according to the Declaration of Helsinki. All participants reported to be right-handed. A structured interview revealed neither a history of neurological or psychiatric illnesses nor any exclusion criteria concerning safety of TMS [23].

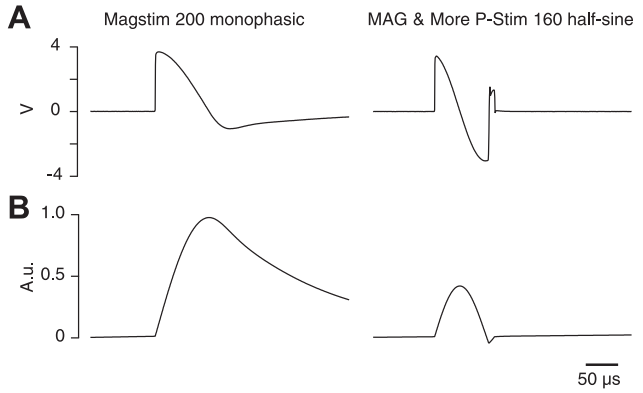

Figure 1. Pulse waveforms. (A) Depicted is the voltage change induced in a probe coil with a diameter of 2 cm and recorded by an oscilloscope (Agilent Technologies MSO7014A, Santa Clara, CA, USA). Intensity was maximum stimulator output. The left panel shows the monophasic waveform (PA current direction) generated by the Magstim 200 stimulator connected to a figure-of-eight coil (type P/N 9925-00 S/N 674). The half-sine waveform (PA current direction) evoked by the MAG & More P-Stim 160 stimulator with a figure-of-eight coil (type 510519m) is depicted on the right. (B) Integral of the induced voltage in (A) (normalized arbitrary units) as estimate of the coil current and the magnitude of the magnetic field strength *B*, which have the same waveform.

Experimental design

We performed two experiments. Experiment 1 investigated the effect of reversing current direction of the paired-pulses on monophasic and half-sine SICF. This experiment consisted of four blocks of SICF according to the two different pulse waveforms (Fig. 1) and current directions, with 10 participants each. For the monophasic waveform, the paired stimuli had identical current direction, i.e., PA–PA or AP–AP. For the half-sine waveform, we used a different stimulation device to apply paired-pulse TMS with two half-sine waves of opposite polarity, i.e., paired PA–AP or AP–PA stimuli. First, we measured RMT with PA and AP current direction (RMT_{PA} and RMT_{AP}), and recorded single-pulse MEPs at stimulation intensity (SI) of 105% RMT_{PA} for PA current as well as 105% RMT_{AP} for AP current. We then probed SICF with S1 and S2 set at 105% of individual RMT. Accordingly, SI for monophasic SICF was 105% of RMT_{PA} for PA–PA and 105% of RMT_{AP} for AP–AP, and for half-sine SICF 105% of RMT_{PA} for PA–AP and 105% of RMT_{AP} for AP–PA.

As a control condition, we designed experiment 2 to account for differences in SI used for SICF with opposite current orientations. Ten volunteers participated in experiment 2, which also consisted of monophasic and half-sine blocks. Due to lower RMT_{PA}, the SI used in experiment 1 for monophasic PA–PA and half-sine PA–AP SICF was lower than for AP–AP and AP–PA measurements. We thus adjusted SI for SICF measurements to 105% of RMT_{AP} and recorded monophasic PA–PA and half-sine PA–AP SICF. This allows a comparison of monophasic PA–PA and half-sine PA–AP SICF recorded at the same SI (105% RMT_{AP}). Before and after probing SICF, we measured RMT_{AP} and recorded 10 single-pulse MEPs at an SI of 105% RMT_{AP} (monophasic PA or biphasic PA–AP pulses). These were used to capture possible shifts in RMT and single-pulse excitability of M1-HAND in response to repetitive application of paired stimuli at short ISIs [24].

Experimental sessions were separated by at least 3 days to avoid possible carry-over effects.

Electromyographic recording

Participants were seated comfortably in an armchair with their stimulated hand resting on a cushion. We recorded MEPs from the

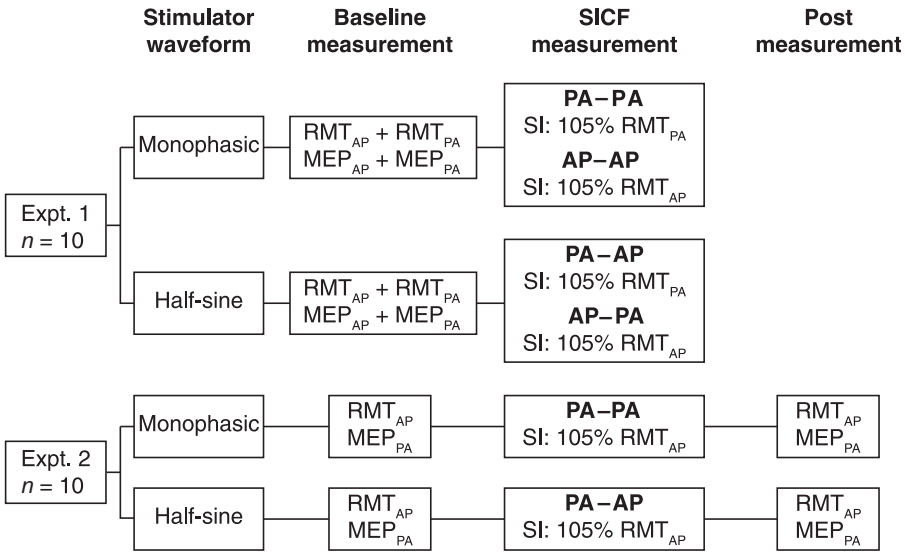

Figure 2. Experimental procedures. We performed two sets of experiments. In experiment 1, we tested the influence of reversing current direction on short-interval intracortical facilitation (SICF) with stimulation intensity (SI) set at 105% RMT_{PA} or 105% RMT_{AP}. We probed SICF using a monophasic (with PA–PA and AP–AP current orientations) or a half-sine waveform (with PA–AP and AP–PA current orientations). Individual RMT_{PA} and RMT_{AP} were determined at the beginning of each session with the stimulator used in the respective session. In experiment 2, we used an SI of 105% RMT_{AP} for PA–PA (monophasic waveform) and PA–AP (half-sine waveform) SICF measurement. This experiment was designed to explore the effect of SI, which differed between current orientations in experiment 1.

left abductor pollicis brevis (APB) muscle at rest by surface electromyography (EMG) using silver/silver chloride electrodes (AMBU, Ballerup, Denmark; surface area 263 mm^2) in bipolar belly-tendon recording technique. Data were band-pass filtered (20–2000 Hz) and amplified (Ekida DC universal amplifier, EKIDA GmbH, Helmstadt, Germany), digitized at a sampling rate of 5 kHz (MICRO1401-mkII, Cambridge Electronic Design Ltd (CED), Cambridge, UK) and stored on a personal computer for online visual display and later offline analysis.

Transcranial magnetic stimulation

We performed TMS with two different stimulation devices: Two Magstim 200 Stimulators connected via a BiStim module (The Magstim Company Ltd, Whitland, UK) generated monophasic TMS pulses (Fig. 1) via a Magstim figure-of-eight coil (outer diameter: 90 mm). And an MAG & More figure-of-eight coil (outer diameter: 100 mm) was attached to a P-Stim 160 Stimulator (MAG & More GmbH, Munich, Germany) to generate half-sine TMS pulses (Fig. 1). The stimulation coil was placed tangentially on the scalp over right M1-HAND with its handle pointing in a posterior direction and laterally at an angle of approximately 45° away from midline. TMS was administered at 0.2 Hz to avoid the induction of any after effects on cortical excitability.

For clarity, current direction always refers to the direction of current induced in M1-HAND. To reverse current direction from PA to AP, we turned the coil by 180° (Magstim 200 Stimulator) or changed waveform polarity (P-Stim 160 Stimulator). Stimulation of the same position was ensured by stereotactic navigation. We asked participants to relax the target muscle throughout the experiment and monitored muscle relaxation using online visual feedback of EMG activity in the target muscle.

At the beginning of each experiment, we determined the optimal site for TMS of right M1-HAND. To this end, we administered clearly suprathreshold single-pulse stimuli inducing an AP current in right M1-HAND. We gradually moved the coil over the presumed M1-HAND representation until we located the position where a single TMS pulse elicited MEPs of maximum amplitudes in the target muscle. We recorded the optimal coil position using a stereotactic, optically tracked navigation system as described [25], and retained position throughout measuring procedures by visual feedback. As a next step, we determined RMT using the adaptive method as recommended [26] with 16 stimuli starting at 45% of maximum stimulator output [27]. The presence of an MEP was operationally defined as compound muscle action potential with peak-to-peak amplitude larger than 50 μV. We measured RMT with AP or PA current orientation, defined as RMT_{AP} and RMT_{PA}. RMT was always determined with the stimulator used in a given session and referenced to maximum stimulator output (MSO) of this device.

Short-interval intracortical facilitation

We assessed SICF in right M1-HAND [28,29] using two suprathreshold stimuli. S1 and conditioning S2 always had the same SI, which was adjusted to individual RMT (105% of RMT, see *Experimental design* and Fig. 2). We chose this SICF protocol [30,31] because the P-Stim 160 stimulator cannot apply paired-pulses with different intensity of each pulse. ISIs between S1 and S2 ranged from 1.0 to 5.0 ms in steps of 0.2 ms, and we recorded 10 MEPs each in pseudo-randomized order. In addition, we measured 10 responses to S1 alone interspersed among the paired-pulse stimuli in each SICF session. We used these unconditioned single-pulse MEPs as baseline to quantify relative MEP facilitation induced by paired-pulse stimulation.

Analyses and statistics

We ensured comparable relaxation in the recorded muscle by rejecting contaminated sweeps online as well as by additionally investigating offline the EMG baseline of every single sweep. Any sweeps showing voluntary EMG activity of more than 50 μV were excluded from analysis. For every ISI, we determined MEP peak-to-peak amplitudes with Signal software version 3 (CED) and calculated the mean of 10 trials. MEP latencies were measured from stimulus artifact to onset of EMG activity by visual inspection and averaged over 10 trials. For each ISI, paired-pulse facilitation was

Table 1
Group data: mean MEP amplitude and ISI for each of the three SICF peaks. We fitted individual SICF data from experiment 1 and 2 with a Gaussian multi-peak curve fit. The table lists mean ISIs and MEP amplitudes of the three SICF peaks revealed by the curve fitting procedure. The error estimate represents SEM. See also Supplementary Fig. S1 for an exemplary illustration.

Experiment	Waveform	Current direction	Stimulation intensity	Peak 1		Peak 2		Peak 3	
				ISI (ms)	Amplitude	ISI (ms)	Amplitude	ISI (ms)	Amplitude
1.1	Monophasic	PA–PA	105% RMT_{PA}	1.32 ± 0.05	2.34 ± 0.40	2.83 ± 0.03	3.09 ± 0.72	4.75 ± 0.10	2.41 ± 0.74
		AP–AP	105% RMT_{AP}	1.35 ± 0.06	7.52 ± 1.99	2.24 ± 0.10	4.13 ± 0.72	4.30 ± 0.07	3.09 ± 0.48
1.2	Half-sine	PA–AP	105% RMT_{PA}	1.25 ± 0.07	1.42 ± 0.33	2.71 ± 0.06	1.44 ± 0.26	4.28 ± 0.16	0.87 ± 0.20
		AP–PA	105% RMT_{AP}	1.44 ± 0.03	2.46 ± 0.67	2.80 ± 0.09	2.14 ± 0.40	4.48 ± 0.12	1.84 ± 0.45
2.1	Monophasic	PA–PA	105% RMT_{AP}	1.22 ± 0.04	1.05 ± 0.20	2.44 ± 0.05	0.87 ± 0.20	4.09 ± 0.11	0.88 ± 0.23
2.2	Half-sine	PA–AP	105% RMT_{AP}	1.23 ± 0.05	2.24 ± 0.39	2.61 ± 0.12	1.45 ± 0.32	4.29 ± 0.12	1.24 ± 0.13

calculated as ratio of the MEP amplitude elicited by paired-pulse stimulation (S1 + S2) over the MEP amplitude elicited by the unconditioned stimulus (S1) alone. For SICF peak analysis, a Gaussian multi-peak curve fitting was performed using Igor Pro 6.32A software (Wavemetrics, Lake Oswego, OR) on individual SICF curves.

We used the SPSS software package for statistical analysis (version 18.0, SPSS Inc., Chicago, IL). Amplitudes and latencies of MEPs elicited by single-pulse TMS and RMT were analyzed via repeated-measures analysis of variance (rmANOVA) with *current direction* (two levels: AP and PA) and *waveform* (two levels: half-sine and monophasic) as within-subjects factors. SICF data were analyzed using a three-factorial rmANOVA with the within-subjects factors *ISI* (21 levels), *waveform* (two levels: monophasic and half-sine), and in-between-subjects factor *current direction* of the first pulse (two levels: AP and PA). Amplitude ratios of SICF peaks were calculated with amplitude parameters extracted from the curve fitting procedure (Table 1). RmANOVA of SICF peak ratios had the within-subjects factors *peak* (three levels: $SICF_2/SICF_1$, $SICF_3/SICF_1$ and $SICF_3/SICF_2$) and *waveform* (two levels: half-sine and monophasic), and the in-between-subjects factor *current direction* of the first pulse (two levels: AP and PA). For experiment 2, rmANOVA included the within-subjects factors *stimulation intensity* (two levels: 105% RMT_{PA} and 105% RMT_{AP}) and *ISI* (21 levels) or *peak* (three levels: $SICF_2/SICF_1$, $SICF_3/SICF_1$ and $SICF_3/SICF_2$). The Greenhouse–Geisser correction was used if necessary to adjust for violations of sphericity, and rmANOVA was followed by two-tailed paired, unpaired or one-sample *t*-tests, where applicable. We also compared mean MEP amplitudes evoked with single-pulse TMS before and after each block of SICF measurements using two-tailed paired *t*-tests. $P < 0.05$ was considered significant and all data are expressed as mean ± SEM.

Results

The effect of current direction and pulse waveform on RMT, single-pulse MEP amplitude, and latency

RMT and single-pulse MEPs are influenced by current orientation and waveform of the TMS pulse [20,21]. Figure 3A shows the effect of current direction and waveform on RMT (rmANOVA; *current direction*: $F_{(1,9)} = 100.59$; $P < 0.00001$; *waveform*: $F_{(1,9)} = 181.72$; $P < 1e^{-6}$; *current direction* × *waveform*: $F_{(1,9)} = 33.52$; $P < 0.001$). RMT was significantly lower when measured with PA current using both waveforms (monophasic: $P < 0.0001$; half-sine: $P < 0.001$; paired *t*-tests).

MEP amplitudes elicited by single-pulse TMS at 105% RMT_{PA} for PA and 105% RMT_{AP} for AP did not differ between PA and AP current direction (Fig. 3B and C). Consequently, rmANOVA results were not significant (*current direction*: $F_{(1,9)} = 0.13$; $P = 0.73$; *waveform*: $F_{(1,9)} = 0.31$; $P = 0.59$; *current direction* × *waveform*: $F_{(1,9)} = 0.32$; $P = 0.59$), which indicates that the difference in efficiency between PA and AP oriented stimuli is mainly due to the RMT differences. In contrast, MEP latencies were consistently influenced by current direction as confirmed by rmANOVA (*current direction*: $F_{(1,9)} = 72.55$; $P < 0.0001$; *waveform*: $F_{(1,9)} = 39.19$; $P < 0.001$; *current direction* × *waveform*: $F_{(1,9)} = 13.92$; $P = 0.005$). MEP latencies were shorter for PA current with both waveforms (monophasic: $P < 0.0001$; half-sine: $P < 0.001$; paired *t*-tests; Fig. 3D), and slightly shorter for monophasic compared with half-sine pulses (PA: $P < 0.001$; AP: $P = 0.005$).

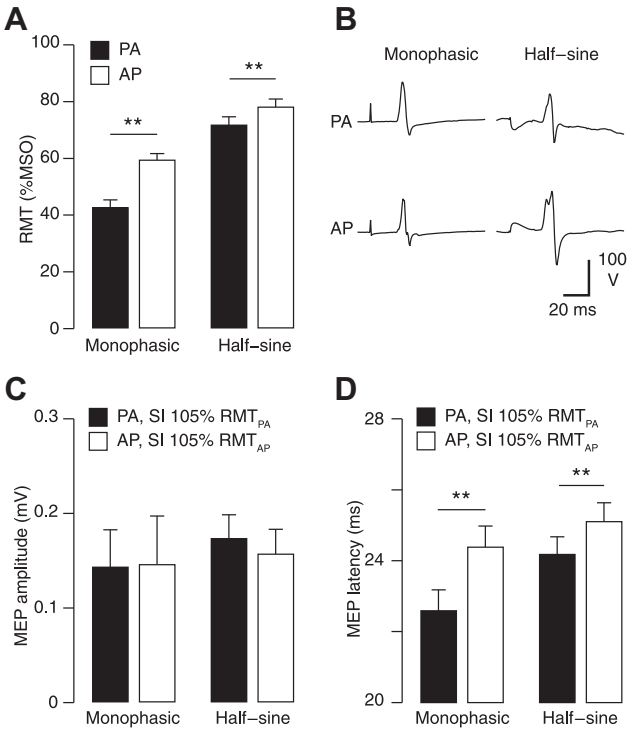

Figure 3. Influence of current direction on RMT, MEP amplitudes and latencies with SI relative to RMT_{AP} and RMT_{PA}. (A) Mean RMT for single-pulse TMS producing a tissue current in M1-HAND with either PA or AP current direction. RMT was significantly lower when determined with PA oriented stimuli ($n = 10$). (B) Representative MEP amplitudes (averages of 10 sweeps each) evoked by single-pulse TMS. MEPs were elicited using monophasic (left) or half-sine stimuli (right). Stimulation intensity was relative to RMT of the induced current direction in M1-HAND, i.e., 105% of RMT_{PA} (top panel) or 105% of RMT_{AP} (bottom panel). (C and D) Mean MEP amplitudes and latencies obtained in experiment 1 ($n = 10$) at a slightly suprathreshold stimulation intensity, which we adjusted to RMT with respect to the induced current direction in M1-HAND (i.e., 105% of RMT_{PA} or 105% of RMT_{AP}). Whereas PA and AP stimuli produced comparable MEP amplitudes, MEP latencies were significantly shorter when TMS induced a PA current in M1-HAND. Error bars denote SEM. $^*P < 0.05$; $^{**}P < 0.01$.

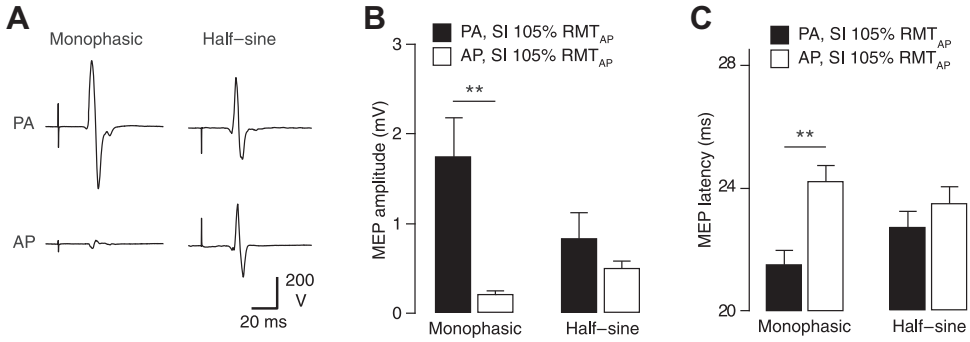

Figure 4. Influence of current direction on MEP amplitudes and latencies with constant SI (105% RMT_{AP}). (A) Representative MEP amplitudes (averages of 10 sweeps each) evoked by single-pulse TMS. MEPs were elicited using monophasic (left) or half-sine stimuli (right). For both current orientations, stimulation intensity was relative to RMT of AP current direction in M1-HAND, i.e., 105% of RMT_{AP}. (B and C) Mean MEP amplitudes and latencies in 10 healthy individuals when using constant stimulation intensity for each of the waveforms (i.e., 105% of monophasic or half-sine RMT_{AP}). A single TMS pulse inducing PA current elicited greater MEP amplitudes with shorter latencies than AP current. For single-pulse TMS analysis, we used the unconditioned MEPs evoked by interspersed during SICF measurements from experiment 2 ($n = 10$). Error bars denote SEM. $^{**}P < 0.01$.

Adapting stimulus intensity to RMT_{AP} for PA and AP oriented pulses

We also analyzed the interspersed single-pulse MEPs during SICF measurements elicited using an SI of 105% RMT_{AP} for PA and AP oriented stimuli in experiment 1 and 2 ($n = 10$). Figure 4 depicts MEP amplitude and latency, which differed greatly when reversing current direction from PA to AP. Accordingly, rmANOVA revealed a significant effect of *current direction* ($F_{(1,9)} = 11.22$; $P = 0.009$) and a significant *current direction* × *waveform* interaction ($F_{(1,9)} = 10.84$; $P = 0.009$), but no main effect of *waveform* ($F_{(1,9)} = 1.90$; $P = 0.20$). MEP amplitudes were larger ($P = 0.005$; paired *t*-test; Fig. 4B) for monophasic PA single-pulse TMS compared to AP, when recorded using 105% of monophasic RMT_{AP}. The difference between PA and AP half-sine single-pulse MEPs elicited with 105% of half-sine RMT_{AP} did not reach statistical significance ($P = 0.19$; paired *t*-test; Fig. 4B).

For MEP latencies, rmANOVA showed a significant effect of *current direction* ($F_{(1,9)} = 96.90$; $P < 0.00001$) and a significant *current direction* × *waveform* interaction ($F_{(1,9)} = 20.21$; $P = 0.001$), but no effect of *waveform* ($F_{(1,9)} = 1.11$; $P = 0.32$). MEP latencies were shorter for monophasic PA single-pulse TMS than for AP current orientation (21.5 ± 0.5 ms vs. 24.2 ± 0.5 ms, $P < 0.001$; paired *t*-test; Fig. 4C). Half-sine MEP latencies were also shorter for PA vs. AP pulses (22.7 ± 0.5 ms vs. 23.5 ± 0.5 ms, $P = 0.055$, paired *t*-test; Fig. 4C).

Stronger directional effects on single-pulse TMS when using a monophasic pulse waveform

As indicated by the *current direction* × *waveform* interactions in the respective rmANOVAs, monophasic vs. half-sine pulse waveform influenced the effect of current direction on MEP amplitude, latency and RMT. For quantification, we analyzed individual differences in MEP amplitude, latency, and RMT between PA and AP oriented stimuli for both waveforms. Figure 5 shows that reversing current direction from PA to AP had a larger effect for monophasic compared with half-sine stimuli, where individual differences were significantly smaller (RMT: $P = 0.0002$; MEP amplitude: $P = 0.009$; MEP latency: $P = 0.002$ and $P = 0.006$; paired *t*-tests).

Impact of pulse waveform and current direction on SICF

Pairs of monophasic pulses induced SICF with three distinct peaks of MEP facilitation at ISIs of approximately 1.4, 2.8 and 4.4 ms. These peaks were separated by troughs showing no or only moderate facilitation (Fig. 6A). SICF was consistently present in the PA–PA and AP–AP condition (Figs. 5A and 6C). Half-sine paired-pulses with opposite current orientation (i.e., PA–AP and AP–PA) elicited similar early MEP facilitation with two distinct SICF peaks at ISIs of approximately 1.4 and 2.8 ms (Fig. 6B). SICF at later ISIs was

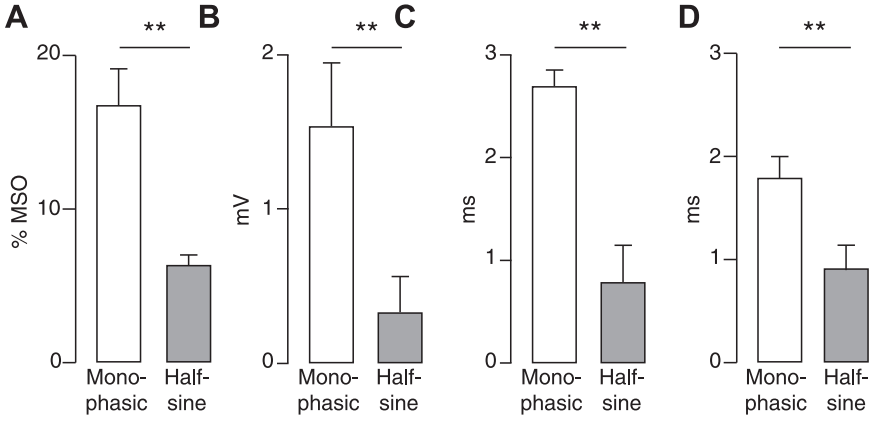

Figure 5. Influence of pulse waveform on differences in RMT, MEP amplitudes and latencies between PA and AP current direction. Shown are mean differences between PA and AP current direction for monophasic and half-sine single pulse TMS. (A) RMT difference in % of MSO of the respective stimulator ($n = 10$). (B) Single-pulse MEP amplitude difference ($n = 10$, data from Fig. 4 (experiment 2)). (C) MEP latency difference ($n = 10$, data from Fig. 4 (experiment 2)). (D) MEP latency difference ($n = 10$, data from Fig. 3 (experiment 1)). The difference between PA and AP current direction was more pronounced when using a monophasic waveform, which suggests a disparity between the two waveforms in terms of preferential generation of I-waves when current direction is inversed. Error bars denote SEM. $^{**}P < 0.01$.

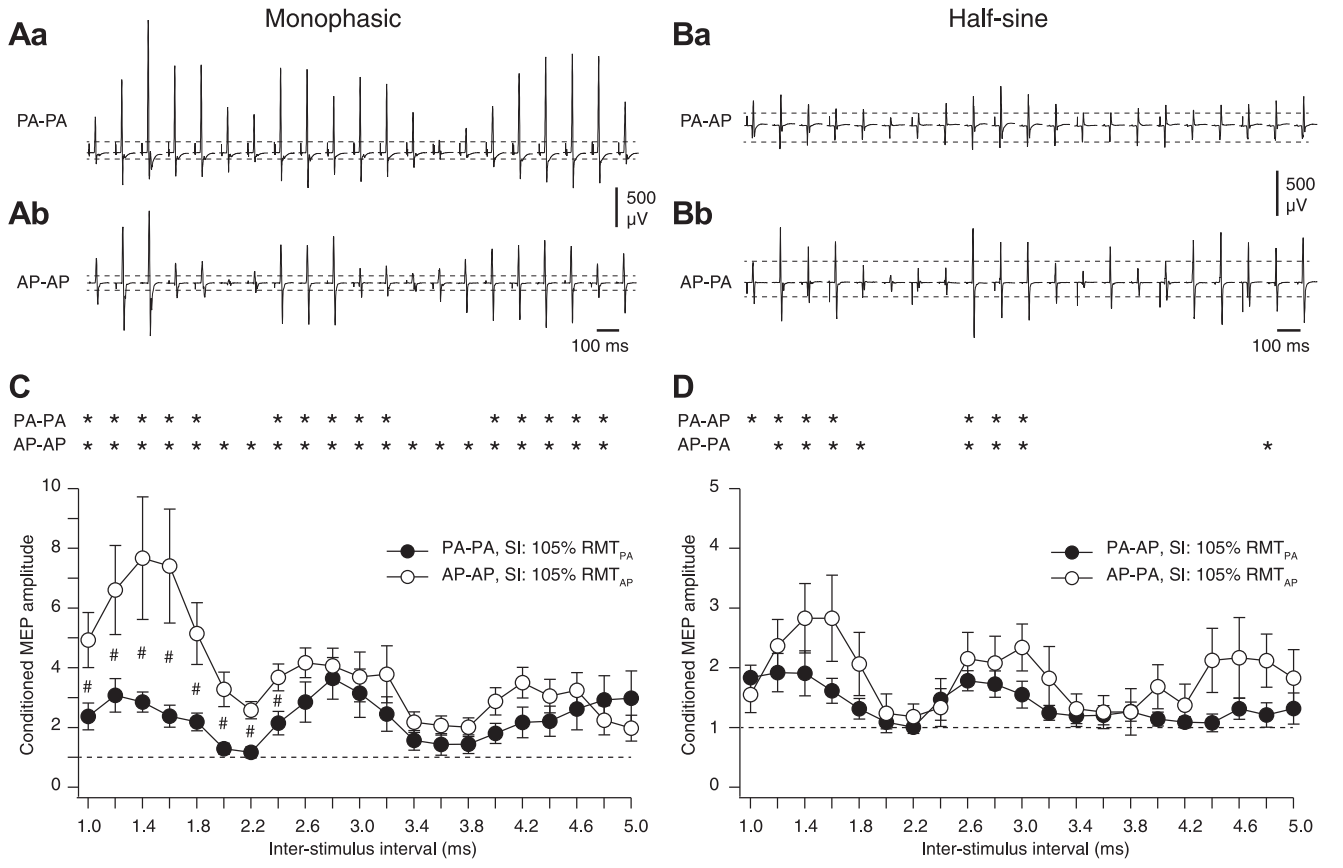

Figure 6. Experiment 1: monophasic and half-sine SICF. (A) Representative MEPs evoked by paired stimuli for all ISI of SICF measurement using monophasic pulse waveform. (Aa) shows PA–PA current direction and (Ab) AP–AP current direction. (B) Representative paired-pulse MEP traces for all ISI of SICF measurement using half-sine pulse waveform. (Ba) depicts PA–AP current direction, and current direction in (Bb) is AP–PA. In (A and B), traces are averages of 10 trials each and dashed lines indicate the size of the corresponding single-pulse MEP amplitude evoked by S1 alone. SICF could be induced using both waveforms. (C) Monophasic SICF. Shown are group data ($n = 10$). For SICF, TMS induced either a posterior–anterior (PA–PA) current (filled circles) or anterior–posterior (AP–AP) current (empty circles) in the stimulated right M1-HAND. We used monophasic pulse waveform and set stimulation intensity at 105% of RMT_{PA} for PA–PA and at 105% of RMT_{AP} for AP–AP current orientations. PA and AP current orientations produced SICF with three distinct peaks. Error bars represent SEM. $^{*}P < 0.05$ compared to single-pulse MEP amplitudes; *top row*: PA–PA; *bottom row*: AP–AP. $^{\#}P < 0.05$ between current orientations. (D) Half-sine SICF. Shown are group data ($n = 10$). For SICF, TMS induced either a posterior–anterior (PA–AP) current (filled circles) or anterior–posterior (AP–PA) current (empty circles) in the stimulated right M1-HAND. We used the half-sine pulse waveform and set stimulation intensity at 105% of RMT_{PA} for PA–AP and at 105% of RMT_{AP} for AP–PA current orientations. Error bars represent SEM. $^{*}P < 0.05$ compared to single-pulse MEP amplitudes; *top row*: PA–AP; *bottom row*: AP–PA.

less pronounced though. Half-sine AP–PA stimulation only induced consistent SICF at a single late ISI (ISI = 4.8 ms), while paired-pulse TMS with PA–AP caused no consistent SICF at ISIs above 3.0 ms.

Using the conditioned MEP amplitude as dependent variable, rmANOVA showed a significant interaction of *ISI* × *waveform* × *current direction* ($F_{(2.4,43.8)} = 3.52$; $P = 0.03$, Table 2). The interaction indicates that the efficiency of SICF may be determined by the combination of current orientations of S1 and S2. To further investigate this effect, we performed separate follow-up rmANOVAs for the two waveforms.

SICF induced by monophasic pulses

Monophasic pulse pairs induced a significant modulation of conditioned MEP amplitudes (main effect of *ISI*: $F_{(2.1,38.2)} = 7.21$; $P = 0.002$), due to the peaks and troughs of the SICF curve (Fig. 6C).

Post-hoc testing revealed significant paired-pulse facilitation for both current directions, with peaks at ISIs of ~1.4, 2.8 and 4.4 ms ($P < 0.05$, Fig. 6C). There was also a trend towards a main effect of *current direction* ($F_{(1,18)} = 4.33$; $P = 0.052$), reflecting a tendency towards stronger SICF for AP–AP stimulation relative to PA–PA stimulation. Critically, there was a significant interaction between *ISI* and *current direction* ($F_{(2.1,38.2)} = 4.06$; $P = 0.023$), indicating that SICF at some ISIs was more strongly modulated by current direction than others. Indeed, post-hoc comparisons of SICF at each ISI showed stronger facilitation for AP–AP current orientation at ISIs of 1.0–2.4 ms (Fig. 6C), covering the first SICF peak. With monophasic stimuli, SI of 105% RMT_{PA} corresponded to 45.4 ± 2.4% of MSO, and 105% RMT_{AP} was 60.1 ± 2.3% (Magstim 200 stimulator).

SICF induced by half-sine pulses

For half-sine SICF, rmANOVA showed a main effect of *ISI* ($F_{(5.9,105.7)} = 5.28$; $P < 0.0001$) on the conditioned MEP amplitude, but not of *current direction* ($F_{(1,18)} = 1.42$; $P = 0.25$) or interaction between *current direction* and *ISI* ($F_{(5.9,105.7)} = 1.65$; $P = 0.14$). Post-hoc testing revealed significant MEP facilitation for both current directions at ISIs of ~1.4 and 2.8 ($P < 0.05$, Fig. 6D). The third peak, however, was only significant with AP–PA current direction ($P = 0.03$ at ISI 4.8 ms) and not with PA–AP ($P = 0.11$ at ISI 4.6). For half-sine stimulation, SI at 105% RMT_{PA} was 75.6 ± 2.7% of MSO, and 105% RMT_{AP} corresponded to 79.4 ± 3.1% of MSO (P-Stim 160 stimulator).

SICF peaks are differentially affected by current orientation

The size of the three SICF peaks differed between current directions for monophasic stimuli. AP–AP oriented pulses produced three differently sized peaks with $SICF_1$ being largest. We calculated

Table 2
ANOVA results for SICF measurements (experiment 1).

	df	*F*	*P*
Conditioned MEP amplitude of SICF			
ISI	2.6, 47.3	10.34	<0.0001*
Waveform	1, 18	12.97	0.002*
Current direction	1, 18	5.58	0.03*
Waveform × current direction	1, 18	1.67	0.21
ISI × current direction	2.6, 47.3	3.88	0.018*
ISI × waveform	2.4, 43.8	3.11	0.045*
ISI × waveform × current direction	2.4, 43.8	3.52	0.03*
SICF peak ratio			
Peak	2, 36	5.07	0.011*
Waveform	1, 18	0.10	0.76
Current direction	1, 18	1.48	0.24
Waveform × current direction	1, 18	5.07	0.037*
Peak × current direction	2, 36	3.20	0.053
Peak × waveform	2, 36	0.66	0.52
Peak × waveform × current direction	2, 36	1.80	0.18
SICF peak ISI			
Peak	1.2, 20.9	443.71	$<1e^{-15}$*
Waveform	1, 18	1.73	0.21
Current direction	1, 18	0.66	0.43
Waveform × current direction	1, 18	8.20	0.01*
Peak × current direction	1.2, 20.9	0.01	0.93
Peak × waveform	1.7, 30.3	1.49	0.24
Peak × waveform × current direction	1.7, 30.3	3.11	0.067

* $P < 0.05$.

peak ratios (i.e., $SICF_1/SICF_2$, $SICF_1/SICF_3$ and $SICF_2/SICF_3$) based on data from the curve fitting procedure for experiment 1 (cf. Table 1 and Supplementary Fig. S1). Using SICF peak amplitude ratios as dependent variable, rmANOVA showed a significant *current direction × waveform* interaction ($F_{(1,18)} = 5.07$; $P = 0.037$, Table 2). Post-hoc testing revealed significant differences between current orientations (AP–AP vs. PA–PA: $SICF_1/SICF_2$: $P = 0.001$, $SICF_1/SICF_3$: $P = 0.04$, and $SICF_2/SICF_3$: $P = 0.82$; unpaired *t*-tests; Fig. 7). In contrast to monophasic SICF, there was no significant difference in half-sine SICF peak ratio between current orientations PA–AP and AP–PA ($SICF_1/SICF_2$: $P = 0.50$, $SICF_1/SICF_3$: $P = 0.77$, and $SICF_2/SICF_3$: $P = 0.16$; unpaired *t*-tests; Fig. 7). But the reduced third SICF peak in the PA–AP condition was reflected in $SICF_1/SICF_3$ and $SCIF_2/SICF_3$ ratios (Fig. 7B and C).

For the ISIs of SICF peaks, rmANOVA revealed a significant *waveform × current direction* interaction ($F_{(1,18)} = 1.50$, $P = 0.01$, Table 2). The latencies of monophasic SICF peaks were similar for AP–AP condition relative to PA–PA condition ($SICF_1$: $P = 0.54$; $SICF_2$: $P = 0.46$; $SICF_3$: $P = 0.26$; unpaired *t*-tests, Table 1). For half-sine SICF, ISI of the first peak was shorter for PA–AP condition relative to AP–PA condition ($SICF_1$: $P = 0.012$; $SICF_2$: $P = 0.20$; $SICF_3$: $P = 0.22$; unpaired *t*-tests; Table 1).

SICF probed with SI adjusted to RMT_{AP} for both current orientations

In 10 participants, SICF was assessed with monophasic PA–PA stimulus pairs at SI of 105% RMT_{AP} (experiment 2) and compared with PA–PA stimulus pairs at 105% RMT_{PA} from experiment 1 (Fig. 8A) to investigate the effect of SI on SICF. Due to the large difference in RMT between PA and AP current orientation, 105% RMT_{AP} (62.8 ± 2.0% MSO) in this session corresponded to 148.4 ± 6.1% of RMT_{PA}. RmANOVA revealed a significant effect of *ISI* ($F_{(2.6,23.3)} = 4.58$; $P = 0.015$) and *stimulation intensity × ISI* ($F_{(3.3,29.9)} = 4.68$; $P = 0.007$), but not of *stimulation intensity* ($F_{(1,9)} = 4.73$; $P = 0.058$). Significant facilitation for SICF with PA–PA stimulus pairs at 105% RMT_{AP} occurred at all three peaks (ISIs of ~1.2, ~2.4, and ~4.0 ms; $P < 0.05$, *t*-test), and paired-pulse facilitation was stronger for $SICF_1$ and $SICF_2$ (Fig. 8A). The reduced magnitude of PA–PA SICF at 105% RMT_{AP} is most likely caused by the higher SI [31]. When analyzing SICF peak ISIs, rmANOVA demonstrated an influence of SI (rmANOVA; *stimulation intensity × peak*: $F_{(1.1,10.2)} = 8.76$; $P = 0.012$). SICF peaks occurred at shorter ISIs when SI was 105% RMT_{AP} ($SICF_1$: $P = 0.081$; $SICF_2$ $P < 0.00001$; $SICF_3$: $P = 0.001$; paired *t*-tests, Table 1 and Fig. 8). Thus, increasing SI causes a shift toward shorter SICF peak latencies for monophasic PA–PA stimuli.

In these 10 participants, half-sine PA–AP SICF was also assessed with SI of 105% RMT_{AP} and compared with PA–AP SICF recorded with 105% RMT_{PA} from experiment 1 (Fig. 8B). For half-sine stimulation, 105% RMT_{AP} (82.4 ± 2.7% MSO) in this session corresponded to 114.5 ± 0.9% of RMT_{PA}. In contrast to monophasic stimulation, this difference is relatively small (cf. Fig. 3A). Accordingly, both types of stimulation (105% RMT_{AP} and 105% RMT_{PA}) produced similar SICF. RmANOVA revealed a significant effect of *ISI* only (*ISI*: $F_{(4.7,42.0)} = 3.79$; $P = 0.007$; *stimulation intensity*: $F_{(1,9)} = 2.62$; $P = 0.14$; *stimulation intensity × ISI*: $F_{(4.5,40.5)} = 0.68$; $P = 0.62$). For SICF with half-sine paired PA–AP stimuli at 105% RMT_{AP}, significant facilitation occurred at ISIs of ~1.4, ~2.8 ms and ~4.8 ms ($P < 0.05$, *t*-test). Half-sine SICF peak ISIs were not affected by SI (rmANOVA; *stimulation intensity × peak*: $F_{(2,18)} = 0.25$; $P = 0.79$).

Comparison of PA–PA and PA–AP SICF recorded at 105% of RMT_{AP} with AP–AP and AP–PA SICF probed at 105% of RMT_{AP}

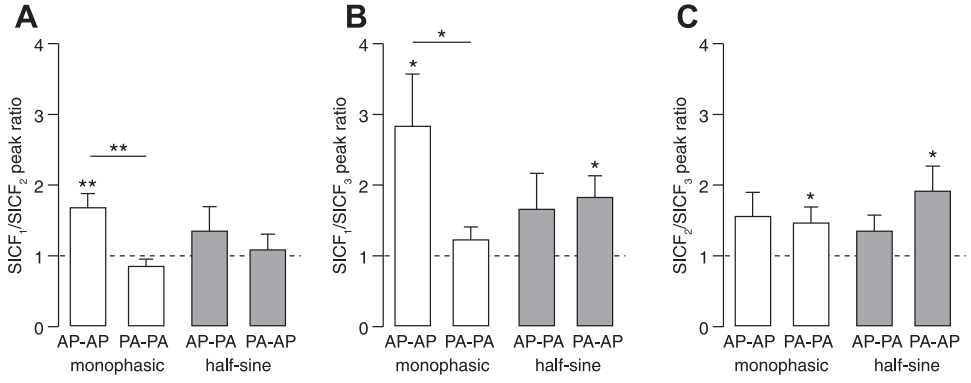

Figure 7. Influence of waveform and current direction on the size of SICF peaks. Individual peak MEP facilitation was extracted from the amplitude parameters yielded by curve fitting (see Methods for details). (A) Peak ratio of the first SICF peak over the second peak ($SICF_1/SICF_2$). (B) Peak ratio of the first peak over the third peak ($SICF_1/SICF_3$). (C) Peak ratio of the second peak over the third peak ($SICF_2/SICF_3$). Monophasic AP–AP stimulation resulted in a modulation of SICF peak sizes by selective enhancement of $SICF_1$. Furthermore, there was a significant difference between current orientations for monophasic pulses. In half-sine PA–AP SICF, the third peak was reduced in size, which is also reflected in the $SICF_1/SICF_3$ and $SICF_2/SCIF_3$ ratios. Bars show mean values with error bars indicating SEM. *$P < 0.05$; **$P < 0.01$.

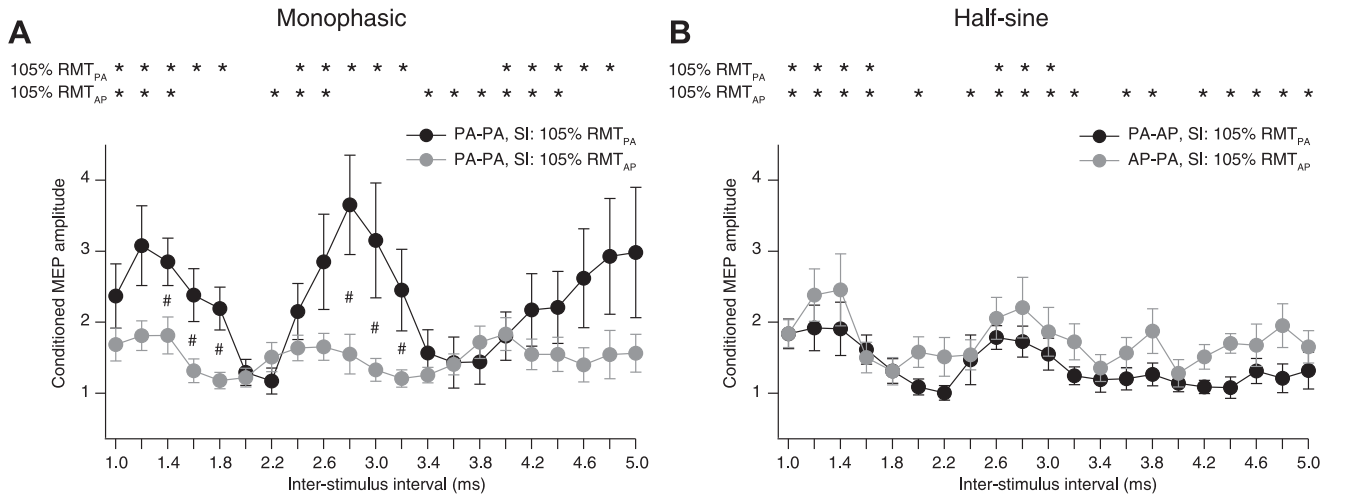

Figure 8. Experiment 2: impact of stimulation intensity on SICF. For monophasic PA–PA and half-sine PA–AP, we also probed SICF with SI set at 105% RMT$_{AP}$. These data were compared with SICF recorded at 105% RMT$_{PA}$ from experiment 1. (A) Monophasic SICF recorded with PA–PA current orientation in M1-HAND and SI set at 105% RMT$_{AP}$ (gray symbols, $n = 10$) and 105% RMT$_{PA}$ (filled symbols, $n = 10$, data from Fig. 6C). Error bars represent SEM. $^{*}P < 0.05$ compared to single-pulse MEP amplitudes; *top row*: PA–PA, 105% RMT$_{PA}$; *bottom row*: PA–PA, 105% RMT$_{AP}$. $^{\#}P < 0.05$ between current orientations. (B) Half-sine SICF probed with PA–AP current orientation in M1-HAND and an SI of 105% RMT$_{AP}$ (gray symbols, $n = 10$) and 105% RMT$_{PA}$ (filled symbols, $n = 10$, data from Fig. 6D). Error bars represent SEM. $^{*}P < 0.05$ compared to single-pulse MEP amplitudes; *top row*: PA–AP, 105% RMT$_{PA}$; *bottom row*: PA–AP, 105% RMT$_{AP}$.

(Supplementary Fig. S3) shows that the impact of current orientation on SICF is at least partly independent of SI.

No lasting effects of SICF measurements on corticospinal excitability

SICF recordings did not alter cortical excitability using either the monophasic or the half-sine waveform (experiment 2, $n = 10$, Supplementary Fig. S2). RMT$_{AP}$ determined with monophasic TMS pulses did not change after monophasic SICF measurements (57.6 ± 2.1% vs. 58.2 ± 2.4% of MSO; $P = 0.45$, paired t-test). And MEP amplitudes elicited with a monophasic PA pulse at an SI of 105% of monophasic RMT$_{AP}$ did not change significantly after SICF (1.27 ± 0.33 mV vs. 1.31 ± 0.36 mV, $P = 0.62$, paired t-test). After half-sine SICF measurements, neither RMT$_{AP}$ determined with half-sine stimuli differed from before (75.8 ± 2.9% vs. 76.0 ± 2.9% of MSO; $P = 0.88$, paired t-test), nor did mean MEP amplitudes elicited with biphasic PA–AP stimuli at an SI of 105% half-sine RMT$_{AP}$ (2.19 ± 0.38 mV vs. 1.91 ± 0.43 mV, $P = 0.45$, paired t-test).

Discussion

Reversing current direction for paired-pulse stimulation impacts on SICF measurement with monophasic and half-sine waveforms. Use of monophasic AP oriented stimuli leads to a strong modulation of SICF peak size, with the first peak of SICF being significantly larger than later peaks. For half-sine stimulation, the third SICF peak is reduced in size with PA–AP current orientation. Before discussing our main results regarding SICF, we would like to address differences between the two waveforms used.

The half-sine waveform is less direction specific

RMT, single-pulse MEP amplitude and in particular MEP latency (direct stimulation effect) provide indirect evidence for recruited I-waves in TMS. The consistent differences for the monophasic waveform confirm earlier observations [7,9,21]. The ~3 ms shorter MEP latency of PA oriented stimuli compared with AP corroborates that *monophasic* TMS preferentially generates early (I_1) or late (I_3) I-waves depending on the induced current direction in M1-HAND [8]. In contrast, direction specific differences in RMT, MEP amplitude, and latency are less pronounced in *half-sine* TMS (Fig. 5), which confirms previous studies probing direction-specific effects of half-sine pulses [21,22]. Particularly the latency difference is smaller (~1 ms, cf. [22]) between current orientations (Fig. 5C and D), which indicates a less direction specific generation of I-waves. Whereas MEP latency for PA oriented half-sine stimuli was longer compared with monophasic PA stimulation (Figs. 3C and 4D), monophasic and half-sine AP pulses elicited MEPs with similar latencies (Figs. 3C and 4D). Single-pulse TMS using PA oriented half-sine waves might thus more likely evoke I_2-waves than I_1-waves. Monophasic and half-sine pulses induce voltage waveforms that differ especially in the second half. The half-sine waveform has a greater negative part [21] and is thus less direction specific than the monophasic waveform. Consequently, half-sine pulses likely generate partly overlapping I-wave patterns with PA and AP current direction. But invasive recordings are needed to clarify the I-wave pattern of half-sine TMS.

Monophasic and half-sine waves elicit SICF

SICF could be probed with monophasic and half-sine waveforms at a relatively strong, suprathreshold SI (Fig. 6). MEP facilitation occurred at ISIs of ~1.4, 2.8 and 4.6 ms, resembling the known latencies of I-waves [2,6,10,32]. To our knowledge, this is the first study using the half-sine waveform to probe SICF in M1-HAND and our results show that paired half-sine pulses can evoke I-wave facilitation. A certain similarity of I-waves evoked by PA and AP current direction might explain why oppositely directed half-sine pulses produce SICF. It further suggests that I-waves induced by PA and AP oriented current have similar excitatory postsynaptic potential (EPSP) summation mechanisms. More generally, the present results implicate that SICF is rather hardwired in the motor cortex and may be relatively easy evoked using different pulse waveforms and current directions. Future studies need to test whether any other TMS waveforms, e.g. biphasic pulses, can also generate SICF.

For monophasic stimulation, PA–PA and AP–AP current directions consistently evoked SICF, which has implications given the

preferential generation of I-waves by monophasic pulses. Although PA and AP preferentially activate different I-waves, they yield SICF with three distinct peaks, indicating that both current directions can activate early and late I-wave circuits in a context of paired-pulse facilitation. However, analyzing the SICF magnitude revealed differential effects depending on current direction.

Impact of current direction on peak specific SICF for monophasic pulses

A modulation of peak sizes with $SICF_1$ being largest occurred in AP–AP SICF but not in PA–PA (Fig. 6). This modulation demonstrates an influence of current direction on SICF and confirms previous studies reporting an enlargement of the first SICF peak by monophasic AP current orientation [30,33]. We show that pairing two single-pulses primarily targeting late I-waves, i.e., inducing AP current, leads to relatively strong facilitation of $SICF_1$, which presumably reflects a facilitatory interaction of early I-wave circuits. At first glance, the strong facilitation for $SICF_1$ may appear counterintuitive. On the other hand, the early I-wave circuit might benefit most from paired-pulse activation, because single AP pulses are usually not suprathreshold to evoke early I-waves. Subthreshold activation results in greater facilitation compared to later SICF peaks, where the later I-wave circuits might be prone to ceiling effects. The hypothesis would fit results from an earlier study [33]. The authors probed monophasic SICF by applying a suprathreshold S1 and a subthreshold S2 using three different combinations (AP–AP, PA–PA, and AP–PA). Hanajima and co-workers proposed that if S1 and S2 induced currents in the same direction, MEP facilitation was produced by summation between EPSPs elicited by the suprathreshold S1 and subliminal depolarization of interneurons elicited by S2 directly [33]. Our results support the assumption that subliminal I-wave activation is important for SICF. Whereas subliminal activation of cortical circuits generating I-waves should not be relevant in single-pulse stimulation, preceding subliminal depolarization of intracortical interneurons by S1 may modulate SICF.

One might expect a strong effect on the third SICF peak when combining two monophasic PA pulses targeting early I-waves, which we did not observe. But I_1-waves are most likely generated downstream from the I_3-circuit [3] and monophasic PA stimulation might, therefore, not be able to significantly influence I_3-waves. On the other hand, the facilitatory interaction occurring at ISIs of ~3 and ~4.5 ms may mainly involve early I-waves.

A recent study investigated the role of preferential I-wave generation in motor cortical plasticity [34]. The authors reported that the relative recruitment of early and late I-waves considerably affects plasticity in M1-HAND. Degree and direction of plasticity induced by theta-burst stimulation depends on which I-waves TMS recruits [34], highlighting the role of different intracortical networks in TMS induced plasticity. Our results demonstrate a similar effect for SICF, where current orientation and hence recruitment of early or late I-waves affects the facilitatory peaks.

Impact of current direction on peak specific SICF for half-sine pulses

In contrast to monophasic paired-pulse TMS, $SICF_1$ was comparable for half-sine PA–AP and AP–PA current orientation. But we did observe that the third peak was not evident for PA–AP SICF. Assuming that PA and AP oriented pulses to some extent generate early and late I-waves preferentially, paired PA–AP pulses at long ISI (~4–5 ms) are unlikely to evoke overlapping I-wave patterns. However, high inter-individual variability might also affect the third peak of PA–AP SICF [33]. For technical reasons, the half-sine paired-pulse stimuli had opposite current directions. At present, paired half-sine AP–AP stimuli cannot be applied at short ISIs. It is thus conceivable that half-sine paired-pulse TMS might exert stronger effects on the magnitude of SICF peaks when the current direction of identical half-sine pulses (AP–AP vs. PA–PA) would be reversed.

Stimulation intensity impacts on SICF peak size and timing

Increasing SI for SICF measurement led to changes in peak size and timing. The effect was more evident for monophasic SICF, where the difference between 105% RMT_{PA} and 105% RMT_{AP} intensities was also greater. When probing monophasic PA–PA SICF at an SI of 105% RMT_{AP}, which corresponds to ~150% of RMT_{PA}, the three peaks were smaller and occurred at shorter ISIs. The effect on the amplitude may be due to ceiling effects of paired-pulse MEP amplitude because SICF depends on SI of S1 and S2 [31]. With higher SI, SICF peaks advanced to shorter ISI, which accords to a previous study [14]. The mechanism for this shift might be recruitment of additional I-waves or even D-waves [35]. For half-sine stimulation, RMT_{PA} and RMT_{AP} differ less. Accordingly, increasing SI to 105% of RMT_{AP} did not change peak ISIs, suggesting that the ~10% difference in SI is not sufficient to recruit additional I- or D-waves. $SICF_1$ and $SICF_2$ peaks were largely unaltered in size by increased SI, but the third peak became prominent. Higher SI may thus be necessary to evoke all peaks of SICF when using half-sine pulses, suggesting that different current directions have variable thresholds for induction of SICF.

Limitations

The comparison of monophasic and half-sine TMS in the present study comprises several limitations. Technical differences between stimulation devices might influence the relative weighting of stimulation of different neuronal elements. Differences in coil design and resonant frequency of the two stimulators may contribute to differences between monophasic and half-sine stimuli. Furthermore, the comparison of monophasic and half-sine SICF may be influenced by differences in the SICF protocols due to technical limitations of the stimulation devices. This mainly applies to the opposite current orientation of half-sine SICF, which leads to differences in current direction and relative SI of S2.

Conclusion

Monophasic pulses are more selective in preferentially evoking early and late I-waves than half-sine pulses. Regarding SICF, both waveforms can induce facilitatory I-wave interaction in M1-HAND by paired-pulses with a relatively strong, suprathreshold intensity. Our results demonstrate that reversing current direction influences the magnitude of SICF peaks with stronger effect for monophasic stimuli. Monophasic AP pulses produce larger paired-pulse facilitation, especially for the first peak. The modulation of peak size suggests that early and late I-waves contribute differentially to SICF peaks. The direction-specific effect of monophasic paired-pulse TMS on the strength of early vs. late SICF thus implies that different cortical circuits mediate early and late SICF.

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Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2013.08.002.

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