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Pulse width biases the balance of excitation and inhibition recruited by transcranial magnetic stimulation

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A single transcranial magnetic stimulation (TMS) pulse is thought to recruit a mixture of excitation and inhibition in human cortex. Therefore, both the assessment of cortical excitability and the response to repetitive TMS protocols depend on the relative recruitment of a range of neuronal populations, each with different physiological characteristics. Currently, the only method for modulating the balance of excitation/inhibition recruited is to manipulate pulse amplitude: some forms of inhibition in primary motor cortex have a lower threshold for recruitment than the excitation involved in generating a motor evoked potential (MEP) [1,2]. Here, we build on recent work showing that other pulse parameters, such as shape and duration, influence the relative recruitment of different *excitatory* neuronal populations [3–5], and test the idea that pulse duration can be used to modulate the relative recruitment of excitation and inhibition.

We used the short-interval intracortical inhibition (SICI) paradigm, where a sub-motor threshold pulse (conditioning pulse) has the effect of suppressing the MEP generated by a subsequent supra-motor threshold pulse (test pulse) delivered a few milliseconds later [2]. Our aim was to examine the effects of different conditioning pulse durations on the level of MEP suppression, with the following rationale. First, we know that motor thresholds vary as a function of pulse duration: brief pulses require greater pulse amplitudes to produce an MEP [3,5]. Second, the amplitude of the conditioning pulse in the SICI paradigm is typically set as a percentage of the motor threshold. The question then is whether different conditioning pulse durations, delivered at the same relative intensity (% motor threshold), produce similar SICI. If they do, then the threshold for inhibition (SICI) and excitation (MEP) would seem to scale with one another across pulse durations, the implication being that the balance of excitation/inhibition recruited by a single pulse is preserved. Alternatively, if the inhibition differs across pulse durations, then excitation/inhibition thresholds do not scale with one another. In this case, different pulse durations presumably recruit a different balance of excitation/inhibition.

28 right-handed volunteers (13 females; age 25 ± 4 years), who reported no contraindications to TMS, participated in two experiments involving TMS over the representation of the right first dorsal interosseous (FDI) muscle. Conditioning pulses were delivered via a figure-of-eight coil (70mm; Magstim Company Ltd, UK) connected to a prototype controllable-pulse parameter TMS device (cTMS3, Rogue Research Inc., Canada; [6]) secured over the top of a flat, elliptical coil connected to a standard TMS device (Magstim 200^2, Magstim Company Ltd., UK) (Fig. 1A), which delivered test pulses. MEPs were recorded via surface electromyography.

Two current directions were applied for the test and conditioning pulses (Fig. 1A), and two pulse durations were used for the conditioning pulses (Fig. 1B). In experiment 1 (n = 15), we assessed SICI at intervals corresponding to the peaks/troughs of each participant's short-interval intracortical facilitation curve (SICF; [7], Fig. 1D), using standard posterior-anterior induced currents and with the FDI muscle at rest. These intervals were chosen to assess whether any differences in SICI between pulse widths could in fact be explained by a differential recruitment of overlapping facilitation [8]. In experiment 2 (n = 15), we wanted to explore the full time course of SICI, which can last up to 20 ms [9]. This is best done with anterior-posterior pulses during weak muscle contraction (10% maximum voluntary electromyogram amplitude [9]), and since we found no evidence of overlapping SICF in experiment 1 (see Fig. 1E), we used a pragmatic range of inter-stimulus intervals up to 20 ms (Fig. 1F).

Resting and active motor thresholds (RMT and AMT) and test pulse intensity, defined at that required to produce a ~1mV MEP at rest in experiment 1 or during voluntary contraction in experiment 2, were determined at the start of each experiment. Following that, a SICI recruitment curve (2 ms inter-stimulus interval, 50–110% AMT conditioning pulse intensities) was generated using the standard TMS device. The relative intensity (%AMT) producing ~50% inhibition (experiment 1) or the greatest inhibition (experiment 2, because SICI can sometimes appear weaker during contraction) was selected for use as the conditioning pulse in the main experiments. Conditioning pulse intensities for brief (30 μs) and long (120 μs) pulses were therefore equivalent in relative terms (%AMT), despite being different in absolute terms (i.e. % maximum stimulator output, %MSO; Fig. 1C). The SICF recruitment curve in experiment 2 was generated using 0.3 ms inter-stimulus intervals, 1mV test pulse and 90%RMT conditioning pulse.

Repeated-measures ANOVA were used to evaluate the influence of pulse width and inter-stimulus interval on SICI (expressed as MEP amplitudes normalised to the amplitude of unconditioned test MEPs). Paired-sample *t*-tests were used to compare stimulus intensities and to follow-up interactions in the repeated-measures ANOVA.

Data are shown mean ± SEM and MEP amplitudes are expressed relative to those obtained with the test pulse alone. Absolute test

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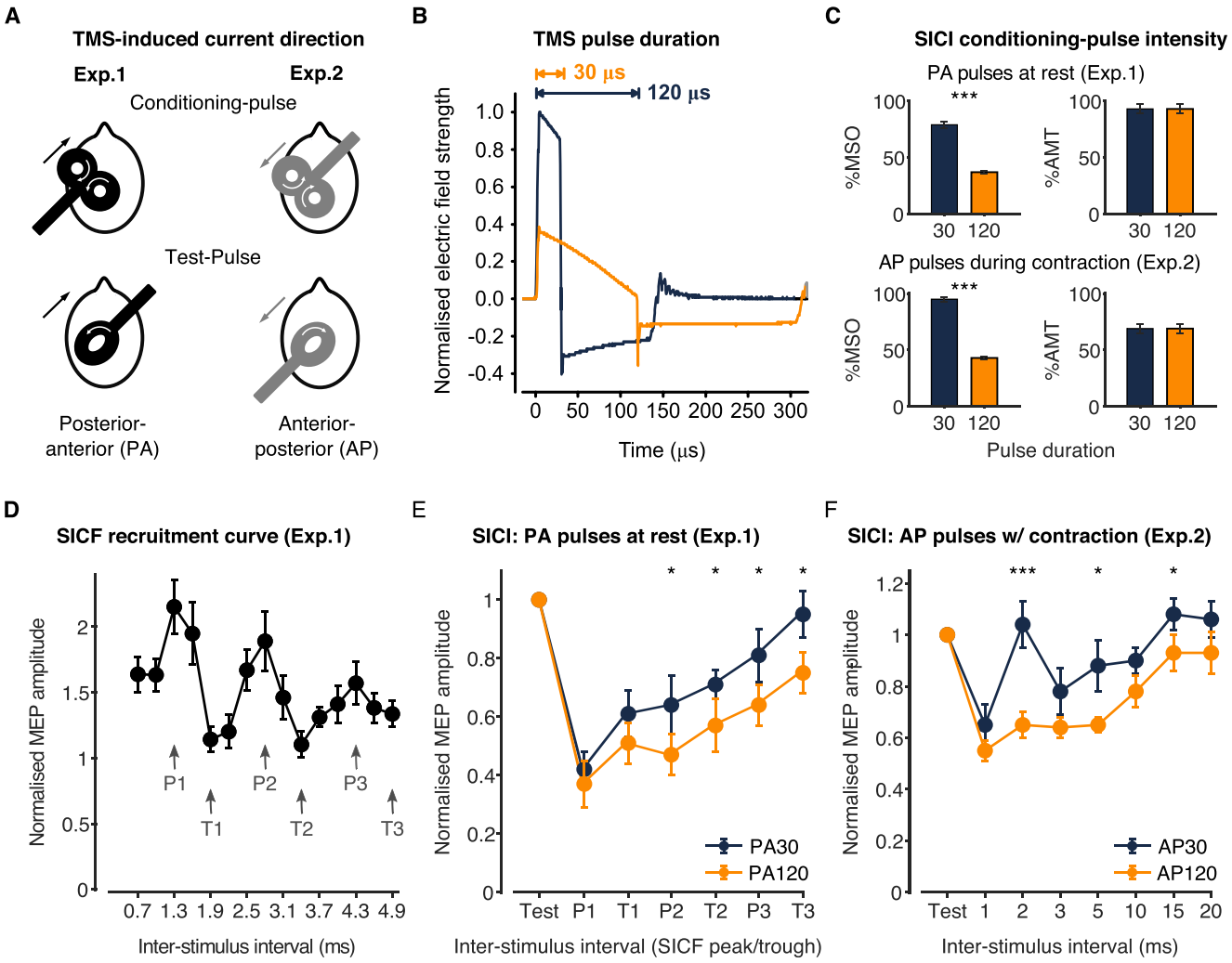

Fig. 1. A. TMS-induced current flow for conditioning pulses and test pulses in the SICI paradigm. Curved white arrows indicate the orientation of current in the coil, whilst the straight arrows indicate orientation of current induced in the brain. The hotspot of the conditioning coil was fixed over the centre-left part of the test coil. **B**. Electric fields induced in a copper wire illustrating the waveform of the short (30 μs) and long (120 μs) duration pulses. **C**. Conditioning pulse intensities in Experiments 1 (posterior-anterior induced current delivered with the muscles at rest) and 2 (anterior-posterior induced current delivered with weak muscle contraction). Intensities were set at an individually determined proportion of active motor threshold. Intensities for each pulse duration were therefore the same in relative terms (%AMT), but differed in absolute terms (%MSO). **D**. SICF inter-stimulus interval recruitment curve illustrating peaks and troughs of facilitation in Experiment 1. These were used to determine the SICI inter-stimulus intervals for each participant (peak 1, trough 1, peak 2, trough 2, peak 3 and trough 3). **E**. SICI in Experiment 1 with posterior-anterior conditioning pulses delivered at intervals corresponding to the peaks and troughs of SICF. Repeated measures ANOVA revealed that short duration pulses elicited less SICI than long duration pulses (main effect of pulse duration: $F_{[1,14]} = 8.426$, $P = 0.012$; main effect of inter-stimulus interval: $F_{[2.79,39.07]} = 14.35$, $P < 0.001$; pulse duration × inter-stimulus interval interaction: $F_{[5,70]} = 0.851$, $P = 0.519$). The fact that the SICI was not systematically different at intervals corresponding to the peaks versus troughs of SICF indicates SICF was not recruited by the conditioning pulses, and thus did not contaminate our assessments of SICI. **F**. SICI in Experiment 2 with anterior-posterior conditioning pulses delivered at intervals up to 20 ms prior to the test pulse. Repeated measures ANOVA revealed that short duration pulses elicited less SICI than long duration pulses (main effect of pulse duration: $F_{[1,14]} = 12.368$, $P = 0.003$; main effect of inter-stimulus interval: $F_{[6,84]} = 8.83$, $P < 0.001$). Moreover, an interaction of pulse duration × inter-stimulus interval ($F_{[3.67,51.34]} = 2.785$, $P = 0.04$) indicated that the recruitment of SICI at 2 ms was particularly weak for short compared to long duration pulses. Significance for paired t-test indicated as follows: $^{***}P < 0.001$, $^{*}P < 0.05$.

pulse MEP amplitudes were similar across different conditions within each experiment (both $P > 0.19$). As expected [3,5], AMT was greater for brief pulses compared to long pulses in each experiment (both $P < 0.001$). Thus, within each experiment, the intensity of the conditioning pulse was greater for brief compared to long pulses in absolute terms (%MSO; Fig. 1C), but identical in relative terms (%AMT; Fig. 1C).

In experiment 1, brief conditioning pulses were associated with less SICI compared to longer pulses (Fig. 1E; see legend for results of ANOVA). In experiment 2, brief conditioning pulses were again associated with less SICI compared to longer pulses (Fig. 1F; see legend for results of ANOVA). However, an interaction of conditioning pulse duration and inter-stimulus interval, also indicated that the reduction in SICI for brief pulses was particularly prominent at 2 ms.

We show for the first time that the extent and duration of SICI is influenced by the duration of the conditioning pulse: brief pulses recruit less pronounced SICI. The reason for this is probably because the neurones responsible for SICI are not the same as those that generate MEPs, and must differ in how they respond to pulses of different duration (i.e. their stimulus strength-duration behaviour [5]). Consequently, setting the conditioning pulse intensity as a proportion of the motor threshold results in differential recruitment of inhibition for different pulse durations. The main implication of

these results is that even when using a single TMS pulse, one will recruit a different balance of inhibition and excitation depending on pulse duration. This could, in part, explain why the outcomes of rTMS differ according to the pulse duration [10]. Additionally, it suggests that, similar to what has been done for excitatory neurones generating the MEP [5], we might now be able to quantify the strength-duration behavior of inhibitory neurones by tracking the threshold required to produce inhibition of voluntary EMG [1] or SICI [2] across pulse durations.

SICI at ~1 ms (including SICF peak 1 in experiment 1) appeared broadly similar across the different pulse widths. This confirms previous work suggesting that its mechanism is different from that at later intervals [2]. Furthermore, given that this early inhibition persists for both directions of current pulses (experiment 1 and 2), it is consistent with the possibility that it relates to the neuronal refractory period [2].

A curious finding was that SICI with brief anterior-posterior directed pulses produced very little inhibition at 2 ms by comparison with the longer-lasting pulse (Fig. 1F). This suggests that brief anterior-posterior conditioning pulses recruit a distinct form of inhibition with a later onset than typical posterior-anterior or even long-duration anterior-posterior pulses, though the issue requires more thorough investigation.

We conclude that pulse duration offers a potential method with which to bias the relative ratio of inhibition and excitation recruited by a TMS pulse, and that this has relevance to assessments of cortical circuitry as well as the outcomes of rTMS protocols.

Declaration of competing interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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