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Pulse Duration as Well as Current Direction Determines the Specificity of Transcranial Magnetic Stimulation of Motor Cortex during Contraction

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ABSTRACT

Background: Previous research suggested that anterior–posterior (AP) directed currents induced by TMS in motor cortex (M1) activate interneuron circuits different from those activated by posterior–anterior currents (PA). The present experiments provide evidence that pulse duration also determines the activation of specific interneuron circuits.

Objective: To use single motor unit (SMU) recordings to confirm the difference in onset latencies of motor-evoked potentials (MEPs) evoked by different current directions and pulse durations: AP_{30}, AP_{120}, PA_{30} and PA_{120}. To test whether the amplitude of the MEPs is differentially influenced by somatosensory inputs from the hand (short-latency afferent inhibition, SAI), and examine the sensitivity of SAI to changes in cerebellar excitability produced by direct current stimulation ($tDCS_{Cb}$).

Methods: Surface electromyograms and SMUs were recorded from the first dorsal interosseous muscle. SAI was tested with an electrical stimulus to median or digital nerves ~20–25 ms prior to TMS delivered over the M1 hand area via a controllable pulse parameter TMS (cTMS) device. SAI was also tested during the application of anodal or sham $tDCS_{Cb}$. Because TMS pulse specificity is greatest at low stimulus intensities, most experiments were conducted with weak voluntary contraction to reduce stimulus threshold.

Results: AP_{30} currents recruited the longest latency SMU and surface MEP responses. During contraction SAI was greater for AP_{30} responses versus all other pulses. Online anodal $tDCS_{Cb}$ reduced SAI for the AP_{30} currents only.

Conclusions: AP_{30} currents activate an interneuron circuit with functional properties different from those activated by other pulse types. Pulse duration and current direction determine what is activated in M1 with TMS.

Introduction

A single TMS pulse over primary motor cortex (M1) activates the axons of excitatory synaptic inputs to corticospinal neurons (CSNs), which initiates descending activity in the corticospinal tract and eventually produces a motor evoked potential (MEP) in contralateral muscles [1]. It is well known that the orientation of the current induced across the central sulcus influences the activation of the CSN [2–4]. Day et al. originally showed that posterior–anterior (PA; Fig. 1) induced-currents gradually recruited indirect wave (I-wave) inputs in order of their appearance (I_1, I_2, I_3 etc.), whilst anterior–posterior (AP) currents preferentially recruited late inputs (I_3) [2], implying that the early (I_1) and late (I_3) I-waves might therefore reflect activity of different excitatory inputs. However, recent accounts suggest that the situation may be slightly more complicated. Ni et al. evaluated the effects of somatosensory inputs from the hand on MEPs (short-latency afferent inhibition, SAI) evoked by different current directions, and found SAI suppressed I_3 waves recruited by PA currents more readily than I_3 waves recruited by AP currents [8]. They concluded that the late I-waves activated by PA and AP current directions were generated by different excitatory inputs. This finding was consistent with recordings of corticospinal activity evoked by AP and PA currents, showing that although

Abbreviations: AP, anterior–posterior; cTMS, controllable pulse parameter transcranial magnetic stimulation device; CSN, corticospinal neuron; MEP, motor evoked potential; PA, posterior–anterior; $tDCS_{Cb}$, transcranial cerebellar direct current stimulation.

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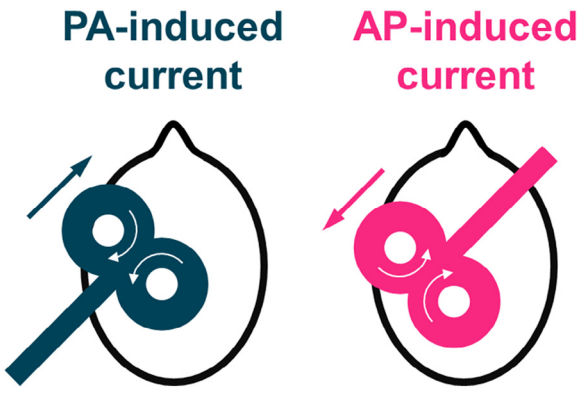

Figure 1. A schematic representation of the TMS coil orientations used. Straight arrows indicate the direction of the current induced in the brain, whilst curved arrows indicate the direction of current in the TMS coil. Posterior–anterior (PA) induced currents in the brain were produced by the coil being oriented posterolaterally at an angle of ~45° to the midline, and anterior–posterior (AP) induced currents in the brain were elicited by placing the coil 180° to the PA currents [2,5–8].

both orientations produce I_1, I_2 and I_3 waves, the peaks are slightly delayed and more dispersed for AP pulses compared to PA pulses.

Using a novel controllable pulse parameter TMS (cTMS; [9]) device, which permits control of the stimulus pulse duration (Fig. 2), we recently found short duration (30 μs) AP currents (i.e. AP_{30}) produced longer latency MEPs than more standard long duration (120 μs) AP (AP_{120}) currents, and thus appeared to activate axons with a delayed input to CSNs [10] (for comparison, traditional pulses are ~82 μs in duration [11]). We had assumed that AP_{30} and AP_{120} currents stimulated the axons of same long latency inputs, but that AP_{30} did so more selectively without also recruiting earlier inputs. Here we tested the hypothesis that the inputs recruited by PA, AP_{120} and AP_{30} currents might actually represent independent circuits by assessing whether they had different functional properties. To do this we evaluated the effects of SAI on MEPs evoked by different combinations of pulse duration and current direction.

Different lines of evidence suggest that the interaction of afferent input with M1 is affected by cerebellar function. First, patients with cerebellar degeneration [12] and Alzheimer's disease [13] exhibit abnormal SAI, and in the latter this is partially restored after cerebellar theta burst stimulation. Second, modulation of cerebellar activity using transcranial direct current stimulation over the cerebellum ($tDCS_{Cb}$) has been reported to reduce the size of AP-evoked, but not PA-evoked, MEPs when assessed during voluntary muscle activation [7]. We therefore tested whether cerebellar excitability changes specifically interacted with SAI evaluated with AP_{120}, AP_{30} or PA_{120} test pulses.

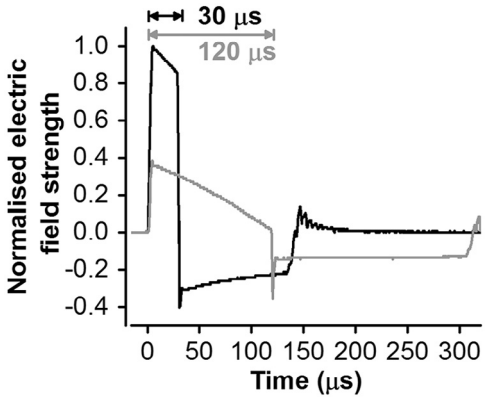

Figure 2. cTMS electric field pulse waveforms for pulse durations of 30 and 120 μs, referring to the duration of the first dominant phase of the electric field, recorded with a search coil and normalised to the maximum amplitude recorded with the 30 μs pulse. The pulse amplitude was limited by the cTMS device to 100 and 37 percent of maximum amplitude for 30 and 120 μs pulses, respectively [9,10].

Methods

Subjects

Twenty-seven volunteers (15 males; age 28 ± 6 years; 25 right-handed), who reported no contraindications to TMS [14], provided written informed consent prior to participating in the study which was approved by University College London Ethics Committee.

Surface electromyogram (EMG)

Surface EMG electrodes (WhiteSensor 40713, Ambu®, Denmark) were placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles of the dominant hand. The ground electrode was over the wrist. Signals were amplified with a gain of 1000 (Digitimer, UK), band-pass filtered (5–3000 Hz), digitised at 5 kHz (1401; CED, Cambridge, UK), and analysed with Signal v5.10 software.

Single motor unit (SMU) EMG

SMU EMG activity was recorded from the FDI of the dominant hand via concentric needle electrodes (25 × 0.3 mm; Ambu®, Denmark). Signals were amplified with a gain of 10,000, band-pass filtered (60 Hz–10 kHz), and sampled at 10 kHz using the same hardware and software as for surface EMG recordings. Auditory and visual feedback of EMG activity helped the subject to maintain the motor unit firing at ~10 Hz.

Transcranial magnetic stimulation (TMS)

MEPs in the dominant FDI were evoked using a custom built cTMS device (cTMS3; Rogue Research Inc., Canada) [9], connected to a standard figure-of-eight coil (wing diameter 70 mm; Magstim, UK). Four combinations of TMS current direction and pulse duration (PA and AP; 30 and 120 μs; Figs. 1 and 2) were applied: AP_{30}, AP_{120}, PA_{30}, and PA_{120}. The motor hot spot was found by searching for the position where slightly suprathreshold PA_{120} currents produced the largest and most consistent MEP in FDI. The position was marked on a cap worn by the participants.

In experiment 1, the test stimulus (TS) intensity required to produce a small increase (~10%) in the SMU firing probability was determined for each TMS pulse type. Otherwise, TS intensity was defined as that required to produce a 1 mV MEP determined either during background contraction (~10% maximum EMG amplitude) (experiments 2 and 4) or at rest (experiment 3). Pulses were given every 3 s (experiment 1) or every 4–5 s (experiments 2–4).

Electrical stimulation

Conditioning stimuli (CS), square wave (0.2 ms) pulses, were delivered to the median nerve at the wrist or to digital nerves of the index and middle fingers via bipolar cup or ring electrodes (cathode proximal) [15], respectively, connected to a constant-current stimulator (DS7AH, Digitimer, UK). Median nerve intensity was just above motor threshold (0.2 mV APB M-wave; Table 2); digital nerve intensity was three times the sensory threshold (Table 2).