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Plasticity induced by pairing brain stimulation with motor-related states only targets a subset of cortical neurones

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Dear editor

Movement-related brain stimulation (MRBS) interventions associate endogenously generated movement-related brain states with external brain stimuli to induce targeted plastic changes in the motor cortex (M1) [1–4]. These studies have emphasised the importance of the timing of stimulation relative to movement onset. However, none has examined whether the effects are specific to the cortical circuits activated by the stimuli.

The question arises because previous work has shown that different sets of inputs to corticospinal neurones can be activated using TMS. Stimulation with a posterior-anterior (PA) direction activates a set of neurones that have a shorter latency connection to corticospinal neurones than those activated with an anterior-posterior (AP) current [5]. Previous MRBS studies have paired movement onset with PA pulses [1]. The present work tests whether the after-effects of MRBS are specific to PA-sensitive neurones, or whether those activated by AP pulses are also affected.

Here we applied AP or PA TMS pulses applied just prior to the onset of volitional index finger movements in two experiments conducted on separate days in the same group of individuals [3]. Corticospinal excitability changes induced by these interventions were assessed using AP and PA TMS pulses in the effector muscle and in a control muscle.

Twenty right-handed volunteers (12 males; ages 20–40) participated in two sessions on different days. Participants filled a written consent form approved by our local ethics committee and following the Declaration of Helsinki. None of the participants had contraindications to TMS.

Participants sat in front of a computer screen with their right-hand index finger resting on a keypad. EMG was acquired from the right hand first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles. Signals were amplified, band-pass filtered (20–2000Hz, Digitimer-D360, Digitimer Ltd, UK), digitised at 5kHz and stored using a Power1401 DAQ controlled with Signal6.2 (CED, UK). TMS was delivered with a 70mm coil (MagPro-TMS, MagVenture, Inc., GA, USA) over the M1-FDI "hot-spot", which was defined as the scalp location resulting in the largest motor evoked potentials (MEPs) with PA and AP currents. The coil was held tangentially on the scalp at an angle of 45° to the mid-sagittal plane.

A warned signal reaction-time task (wSRTT) was used for the intervention [6]. Each trial in the wSRTT consisted of five phases: 1) resting phase (500 ms); 2) warning stimulus (WS, 500 ms); 3) delay period (1000 ms); 4) reaction phase triggered by a "Go" cue; and 5) feedback phase showing participants their reaction time (Fig. 1). Since TMS can delay movements in a wSRTT [7], feedback was omitted in the trials in which TMS was delivered (see below).

Sessions began with wSRTT familiarization, followed by 20 additional trials used to estimate the participants' EMG-based reaction time (RT, see below). The TMS resting motor threshold (rMT) and 500μV intensity (500T) were estimated for PA and AP TMS. They were defined as the lowest stimulus intensities eliciting MEPs with peak-to-peak amplitudes over 50μV (rMT) and 500μV (500T) in 5 out of 10 trials each. The active motor threshold (aMT) was also estimated. For this, subjects were asked to generate a mild sustained contraction (200μV) with the FDI and the minimum TMS intensity at which MEPs with a peak-to-peak amplitude above 200μV could be distinguished was estimated for PA and AP directions. Latencies of the FDI MEPs generated using PA and AP TMS were determined in two blocks of 20 pulses. For this, participants generated mild sustained contractions (200μV) with the FDI and stimuli were given at 110% of the aMT for PA and AP currents. Then, 500T TMS with PA and AP orientations were used to record MEPs before (PRE; 40 pulses), after (POST0; 20 pulses) and 15min after (POST15; 20 pulses) the interventions. Interventions consisted of 3 blocks of 80 trials of the above described movement task wherein a TMS pulse at 110% of the rMT was triggered 30 ms before the estimated RT in 90% of the trials.

RTs were defined as the average time when the rectified and smoothed EMG exceeded five times the amplitude at rest [3]. RTs were compared between interventions using a paired *t*-test. rMT and 500T were compared separately using two repeated measures ANOVAs (rmANOVA) with factors INTERV-DIR (PA vs AP TMS paired with movements) and ASSESS-DIR (pre-/post-intervention MEPs using PA vs AP TMS). MEP latencies were estimated via visual inspection on a trial-by-trial basis [8]. PA- and AP- induced MEP latencies were compared with a paired *t*-test. For this, data were averaged across sessions. Changes in MEP amplitudes across interventions were assessed with a 4-way rmANOVA with factors INTERV-DIR (PA, AP), ASSESS-DIR (PA, AP), MUSCLE (FDI, ADM) and TIME (PRE, POST0, POST15). Paired *t*-test comparisons with Bonferroni corrections were used for post-hoc comparisons. Normality was checked by assessing that z-scores of the

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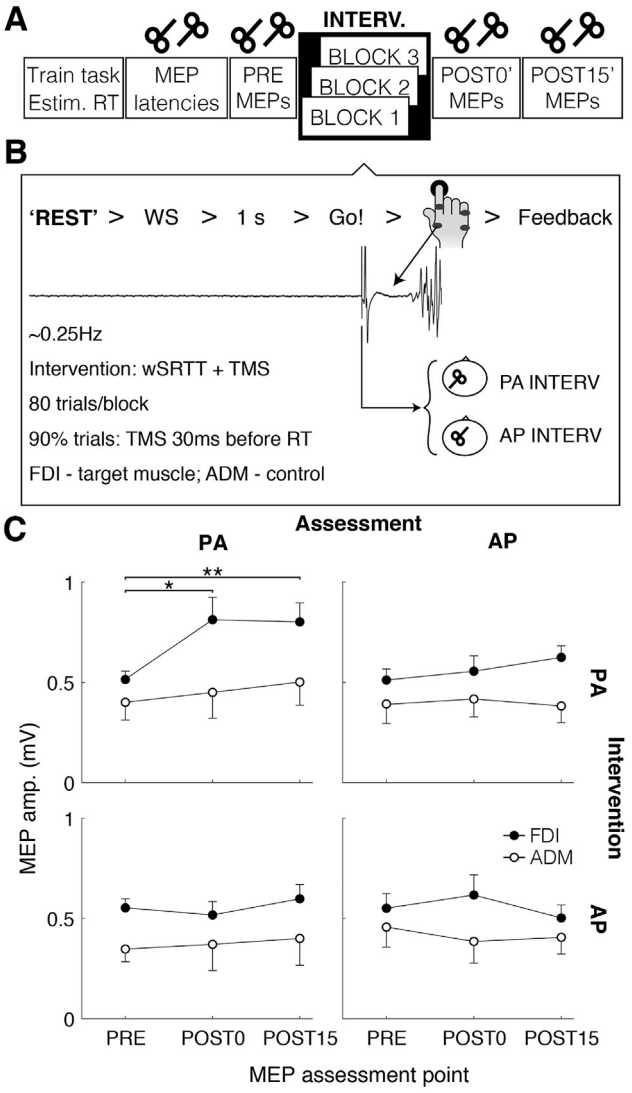

Fig. 1. Effects of pairing movement initiation with directional TMS on PA- and AP-sensitive corticospinal circuits. (A) Schematic representation of the experimental sessions and description of the movement task used to associate movement initiation-related brain states with TMS in the PA or AP direction. Each session started with a phase in which participants trained the wSRTT. Once they reached a consistent behaviour, their RT was estimated. Then, MEPs were acquired by delivering TMS pulses in PA and AP directions and with 110% aMT intensities. This allowed us to determine the latencies of the evoked PA-/AP-MEPs. (B) Structure of the intervention trials together with an example of an EMG trace recorded from the FDI when TMS was delivered 30 ms before the expected RT. Recording electrodes were placed on the muscle bellies, with reference electrodes on the closest metacarpophalangeal joints. The ground electrode was placed on the right wrist. Trials began with an initial resting stage, during which the word "Rest" appeared onscreen for 500 ms. Following the rest phase, a warning signal (WS; a red circle in the center of the screen) appeared for 500 ms. The WS informed subjects to be ready to move as fast as possible in reaction to the forthcoming 'Go' signal. Then the screen went blank for 1000 ms. The "Go" signal (green circle in the center of the screen) was presented after this period of time and it was kept until the participant pressed a button on an experimental keypad. Feedback was then given depending on how soon after "Go" signal participants pressed the button, as detailed previously [7]. (C) Changes in MEP amplitudes as a result of the intervention (mean±SEs). FDI (black circles) and ADM (white circles) represent MEP amplitudes in the PA (upper graphs) and AP (bottom graphs) conditions. MEPs assessed using PA and AP currents are plotted on the two left and two right graphs, respectively (*P < 0.05, **P < 0.01).

populations' kurtosis and skewness were below a critical value of 2 [9]. Results are provided as mean ± SD and effects are considered significant when $P < 0.05$.

There were no significant differences between RTs in the PA (210 ± 18 ms) and AP (203 ± 13 ms) interventions (Supp. Table 1). TMS pulses were delivered before muscle activation in 95 ± 22% and 93 ± 25% of the trials in the PA and AP interventions. This anticipatory feature of stimuli has proven to be important to ensure induction of plastic effects in these interventions [3]. rMT and 500T with PA currents were 49 ± 9% and 57 ± 9% of the maximum stimulator output. rMT and 500T with AP currents were 68 ± 9% and 80 ± 13%. There was a significant effect of ASSESS-DIR on the estimated rMT ($F_{[1,19]} = 134.875$; $P < 0.001$; $\eta 2 = 0.878$) and 500T ($F_{[1,19]} = 197.099$; $P < 0.001$; $\eta 2 = 0.912$) (Supp. Table 1). MEP latencies induced with PA currents (22±1 ms) were significantly shorter (~2 ms) than those induced with AP currents (24±2 ms) ($P < 0.001$; Supp. Table 2).

Fig. 1 and Supp. Table 3 show the changes in FDI and ADM MEP before and after the interventions and the results of the rmANOVA. There was a significant MUSCLE*TIME interaction ($F_{[2,36]} = 7.157$; $P = 0.002$; $\eta^2 = 0.285$). Paired comparisons between time points indicated a significant difference between FDI MEPs at PRE and POST15 ($P = 0.026$). Importantly, there was a significant INTERV-DIR*ASSESS-DIR*MUSCLE*TIME interaction effect ($F_{[2,36]} = 9.171$; $P = 0.001$; $\eta^2 = 0.338$). Post-hoc comparisons revealed significant differences only for the PA intervention and for FDI MEPs probed with PA TMS. These differences were between PRE and POST0 (P=0.015) and PRE and POST15 (P=0.007).

In summary, we tested whether MRBS interventions interact differentially with two independent circuits activated by TMS. The results showed that plastic changes could only be observed in PA-induced MEPs and only when PA currents were used in the intervention. This selectivity suggests that TMS can target specific cortical neurones when stimuli are given during movement initiation. The simplest explanation for this is that paced flexion of the index finger activates a population of neurones that is also sensitive to PA stimulation, but is relatively insensitive to AP stimulation. Repeated activation of these shared elements then allows some synaptic connections to be strengthened, resulting in increased excitability to PA-TMS.

Given the specificity of the changes observed here, future research should be dedicated to study if this intervention only benefits performance of particular types of movement or if MRBS using a different movement paradigm could only engage AP-sensitive circuits, and benefit a different type of performance.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.12.014.

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