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Driving associative plasticity in premotor-motor connections through a novel paired associative stimulation based on long-latency cortico-cortical interactions

Repeated pre- and post-synaptic neuronal activation is fundamental for strengthening synaptic connections, a key mechanism referred to as spike-time-dependent plasticity (STDP) [1]. In humans, associative plasticity with STDP properties can be induced through a TMS protocol, named cortico-cortical paired associative stimulation (ccPAS) [2–4]. By administering repeated pairs of TMS pulses over two interconnected brain areas at specific inter-stimulus intervals (ISI), ccPAS allows for the modulation of cortico-cortical connections efficiency.

To date ccPAS has been predominantly applied to cortico-cortical motor pathways [2–4]. For example, following ventral premotor-to-motor cortex (PMv-to-M1) ccPAS, scholars documented a strengthening of the targeted circuit, indexed by the increase of the (inhibitory) effect of PMv conditioning over ipsilateral M1 excitability at rest [2] and the increase in resting-state connectivity of the broader functional network encompassing PMv-M1 areas [3]. Effects of increased connectivity are long-lasting [2,4], anatomically specific [2,3] and associated with functionally specific behavioral gains [4].

All the aforementioned studies reported plastic effects induced by ccPAS when the selected ISI met the temporal rules of short-latency (supposedly direct) connections, informed by dual-site TMS (dsTMS) [5]. Notably, recent dsTMS studies tested the chronometry of PMv-to-M1 interactions and showed that they occur at different time scales [5–7]. For example, conditioning PMv was found to reduce the size of motor-evoked potentials (MEPs) induced by stimulation of ipsilateral M1 not only at a 8-ms ISI (short-latency interaction) [5], but also at longer (e.g., 40-ms) ISIs [6], thus demonstrating long-latency, likely indirect, inhibitory PMv-to-M1 interactions.

Despite this notion, there is no evidence that ccPAS protocols based on long-latency interactions (i.e., ll-ccPAS) can induce associative plasticity in humans. Here we empirically address this question by testing the effect of 3 ll-ccPAS protocols on PMv-M1 interactions in healthy volunteers (see Supplementary information for details on methods). In the PMv-to-M1 ll-ccPAS group (N = 12), we continuously administered 90 pairs of TMS pulses over the left PMv and the left M1 at a rate of 0.1 Hz [2–4]. For each pair, PMv preceded M1 stimulation by 40 ms. Such ISI was aimed at activating long-latency PMv-to-M1 inhibitory connections [6]. To test for neuroanatomical specificity [2], we administered the same ll-ccPAS protocol over a parallel pathway connecting the supplementary motor areas (SMA) to M1 (i.e., SMA-to-M1 ll-ccPAS; N = 12). Lastly, to control for unspecific effects, we administered sham ll-ccPAS (N = 12).

To assess for the effect of ll-ccPAS across the 3 groups, we probed long-latency PMv-M1 interactions on MEP amplitudes using the dsTMS protocol [6,7] in 5 blocks (every 20 minutes): 2 prior to (pre-A, pre-B) and 3 following (T0, T20, T40) ll-ccPAS. Each block included both single-pulse trials, in which a test stimulus (TS) was applied alone over the left M1 to measure baseline MEPs, and paired-pulse trials, in which a conditioning stimulus (CS) applied over the left PMv –activating pathways to M1– preceded the TS by 40 ms [6], thus probing long-latency inhibitory effects that PMv conditioning exerts over M1 excitability. In all protocols, the left M1 was identified as the motor hotspot of the first dorsal interosseous (FDI) and stimulated using an intensity adequate to induce a MEP amplitude of ~1 mV in the right FDI, while MEPs were concurrently recorded in a control muscle (abductor digit minimi, ADM). Premotor areas were identified as in Ref. [4,6,7] (Fig. 1A) and stimulated at 90% of the FDI resting motor threshold. Participants were at rest during the whole experiment.

We computed the differences between log-transformed peak-to-peak mean MEP amplitudes in the CS-TS and TS trials and analyzed such differences with a Protocol (PMv-to-M1, SMA-to-M1, Sham) × Time (pre-A, pre-B, T0, T20, T40) × Muscle (FDI, ADM) ANOVA. The analysis showed a significant 3-way interaction ($F_{8,128} = 2.07$, $p = .043$, $\eta_p^2 = 0.11$).

Follow-up analysis revealed that prior to the ll-ccPAS protocols the 3 groups showed comparable MEPs amplitudes (all $p > .10$). Importantly, following ll-ccPAS, MEPs were differently modulated according to the stimulation group. Both active protocols led to enhanced inhibitory interactions but at different timings in the target muscle, whilst no changes in the sham group were observed over time (Table S1). Specifically, the PMv-to-M1 group showed an increased magnitude of PMv-to-M1 inhibitory interactions selectively for the FDI and exclusively at T0 ($p < .02$; Fig. 1B), thus demonstrating that ll-ccPAS can induce associative plasticity in humans. However, in contrast to short-latency ccPAS protocols [2,4], ll-ccPAS effects on PMv-to-M1 network were much more transient as we could not observe them at T20 or T40. Remarkably, while these plastic effects were anatomically specific at T0 (SMA-to-M1 ll-ccPAS did not lead to any significant FDI MEP modulation as in Ref. [2]), SMA-to-M1 ll-ccPAS increased PMv-to-M1 inhibitory interactions at T20 ($p < .03$; Fig. 1C). Thus while short-latency ccPAS seems to leave the coupling of unstimulated premotor-motor pathways unaltered [2] or weakened [3], here we show that ll-ccPAS

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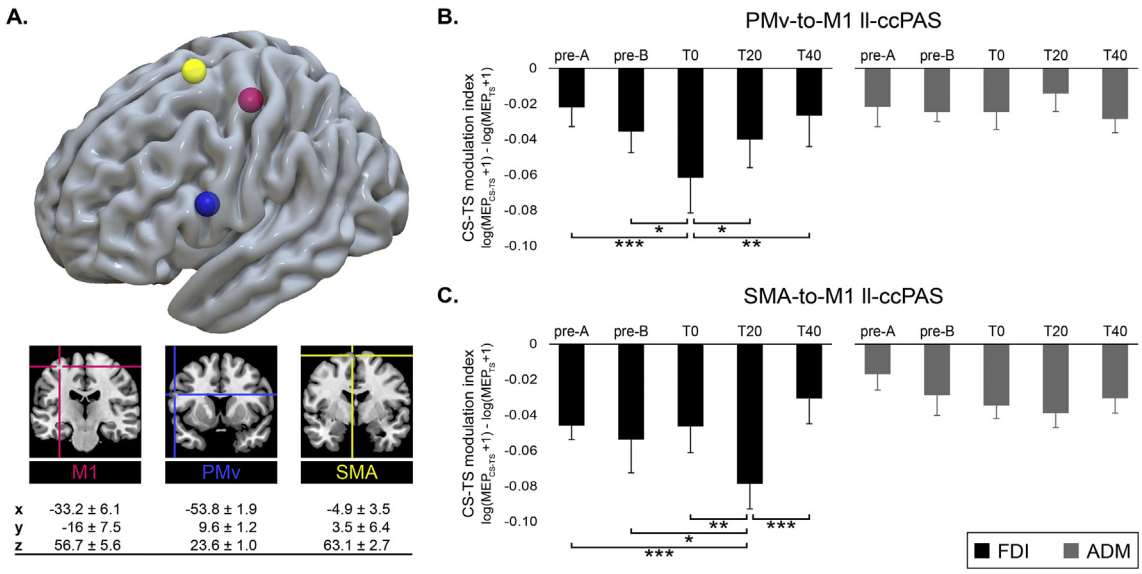

Fig. 1. Talairach coordinates of the targeted cortical sites reconstructed using Surf Ice (https://www.nitrc.org/projects/surfice) (A). Changes in the strength of PMv-to-M1 interactions following PMv-to-M1 (B) and SMA-to-M1 (C) ll-ccPAS. Error bars denote s.e.m. * = p < .05; ** = p < .01; *** = p < .001.

over SMA-to-M1 can transiently enhance long-latency interactions between the unstimulated PMv and M1, although in this case plastic effects took longer to build-up. Spreading of associative plasticity might be due to the activation of indirect pathways: i.e., during SMA-to-M1 ll-ccPAS, the cortical volley elicited by SMA stimulation (first TMS pulse) could recruit PMv [8,9] before reaching M1 at 40 ms (second pulse), resulting in a convergent M1 activation that could strengthen a wider circuit encompassing PMv-to-M1 connectivity. Yet, it is important to note that the different temporal evolution of indirect (SMA-to-M1) and direct (PM-to-M1) associative stimulation impact on MEP amplitudes together with the lack of MEP modulation following sham stimulation, rule out unspecific effects.

In sum, we show that a novel ccPAS tuned to informed long-latency interactions [6,7] is effective in modulating premotor-motor long-latency connectivity. Further studies are needed to determine whether ll-ccPAS also affects short-latencies interactions. Our study suggests that ll-ccPAS can strengthen wider networks through indirect pathways modulations, a feature that might be desirable for efficient modulation of network-to-network connectivity [8,10] engaging complex brain functions.

Credit author statement

Conceptualization: AA, VR; Formal analysis: CE, SB; Funding acquisition: AA, SB, VR; Investigation: CE, SB; Methodology: AA, CE, SB; Software: CE, SB; Visualization: CE, MM, ST; Roles/Writing - original draft: AA, MM, ST; Writing - review & editing: CE, SB, MM, ST, VR, AA.

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.08.003.

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