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Correspondence

Strengthening functionally specific neural pathways with transcranial brain stimulation

Emilio Chiappini[1,2], Juha Silvanto[3], Paul B. Hibbard[4], Alessio Avenanti[1,2] and Vincenzo Romei[1,4]

Cortico-cortical paired associative stimulation (ccPAS) is a recently established offline dual-coil transcranial magnetic stimulation (TMS) protocol [1–3] based on the Hebbian principle of associative plasticity and designed to transiently enhance synaptic efficiency in neural pathways linking two interconnected (targeted) brain regions [4,5]. Here, we present a new 'function-tuning ccPAS' paradigm in which, by pairing ccPAS with the presentation of a specific visual feature, for example a specific motion direction, we can selectively target and enhance the synaptic efficiency of functionally-specific, but spatially overlapping, pathways. We report that ccPAS applied in a state-dependent manner and at a low intensity selectively enhanced detection of the specific motion direction primed during the combined visual-TMS manipulations. This paradigm significantly enhances the specificity of TMS-induced plasticity, by allowing the targeting of cortico-cortical pathways associated with specific functions.

One important use of TMS in humans is the induction of neural plasticity [5]. TMS-induced plastic changes have been implemented by targeting individual cortical areas, and more recently, neural pathways [5]. Yet, an important limitation of TMS paradigms is their approximation of spatial specificity and lack of functional specificity [6]; these paradigms are thus non-specific with regards to

the functional type of neurons they target within the stimulated area. Ideally, one would be able to induce plastic changes in functionally-specific neuronal representations and pathways.

To achieve this goal, we have introduced 'function-tuning ccPAS' with the aim of experimentally strengthening cortico-cortical neural pathways coding for a particular motion direction. We focused on reentrant projections from the motion selective area V5/MT+ to the early visual cortex (V1/V2) that are known to be relevant for carrying visual motion information [7] and to be susceptible to plastic modifications [3]. Crucially, during the ccPAS protocol (see Supplemental Information), participants were presented with a visual motion stimulus moving in a specific direction (either leftwards or rightwards; Figure S1). This manipulation aimed at engaging direction-specific neurons while concurrently activating the pathway between V5/MT+ and V1/V2, so to induce Hebbian-plasticity in functionally-specific reentrant projections.

Sixteen healthy volunteers performed a motion discrimination task before and after the ccPAS protocol — trials could be congruent or incongruent with the motion direction presented during ccPAS — to assess their change in sensitivity to motion direction following ccPAS (Figure 1A). ccPAS repeatedly activated the V5/MT+-V1/V2 neural pathway. We included conditions in which TMS was applied first over V5/MT+ and then, after 20 ms over V1/V2 [3]. TMS was applied over V5/MT+ at 80% of phosphene threshold (PT; Experimental condition; eV5-V1_80), chosen as the optimal intensity needed to selectively engage those neurons preactivated by the moving stimulus, or 100% PT (Control-1; cV5-V1_100), to control for state-dependent mechanisms based on stimulation intensities (see Supplemental Information for details). We included a further condition (Control-2; cV1-V5_80) to control for directionality of stimulation in which V1/V2 preceded V5/MT+ stimulation by 20 ms. Presentation of either leftward or rightward motion stimulus was paired with the ccPAS stimulation (Figure S1).

A repeated measures ANOVA on baseline-corrected motion sensitivity with the factors Session (eV5-V1_80, cV5-V1_100, cV1-V5_80) and Direction (Congruent, Incongruent) revealed a significant two-way interaction ($F_{2,30}$ = 3.86, p = 0.032, η_p^2 = 0.2; other ps > 0.23). Planned comparisons with Bonferroni corrections (Figure 1B) showed a significant change in motion sensitivity threshold following the congruent but not the incongruent direction in the experimental session only (Congruent versus Incongruent (mean ± s.e.m.) –3.42 ± 1.29% versus –0.46 ± 0.95%, p = 0.035, *d* = 0.49). Moreover, the congruent stimuli in the experimental condition (eV5-V1_80: –3.42 ± 1.29%) showed a stronger impact of ccPAS relative to the congruent stimuli presented in all the other control conditions (cV5-V1_100: –0.19 ± 0.7%, p = 0.018, *d* = 0.67; cV1-V5_80: 0.3 ± 1.39%, p = 0.019, *d* = 0.66; for non-baseline-corrected results see Figure S2).

Our key result was the increased performance selective for the motion stimulus direction viewed during the application of ccPAS (congruent motion stimuli). No effect was found for the motion direction opposite to that viewed during ccPAS (incongruent motion stimuli). Furthermore, this effect was specific for the direction of ccPAS (only found for V5/MT+-to-V1/V2 stimulation, in keeping with previous evidence [3,7]). Importantly, this effect was found only for V5/MT+ subthreshold stimulation intensity. This pattern of results is likely to reflect a summation between the impact of TMS and the visual presentation of motion during the ccPAS protocol. Specifically, low intensity TMS is likely to activate selectively those neurons primed by the concurrent visual stimulus [8] whereas it may not be sufficient to activate neurons which have not been pre-activated by the visual stimulus. Thus, only neurons (and their connections) fuctionally tuned to the presented stimulus would be sensitive to TMS, leading to direction-selective induction of plasticity in reentrant V5/MT+-to-V1/V2 connections. Conversely, TMS applied at a higher intensity is sufficient to activate neurons regardless of whether they have been activated by the visual stimulus. While in our previous report [3]

high-intensity TMS led to a general motion sensitivity enhancement irrespective of the motion direction, no net impact of ccPAS on plasticity for high-intensity TMS was found in the current study.

The relevant difference between the two studies is that, previously, ccPAS was applied at rest [3], whereas here ccPAS was applied in a state-dependent manner [6]. Under these circumstances, during high-intensity TMS, lateral inhibition processes physiologically engaged during the motion stimulus presentation [9] are likely to interact with those neuronal pools not tuned to the congruent direction. Therefore, both the congruent and incongruent pathways are likely activated by the TMS pulse but also suppressed by lateral inhibition phenomena, a competitive process resulting in a net zero-effect, resembling the 'reset' TMS effect observed in some TMS-adaptation paradigms [6]. Finally, given the central positioning of the V1/V2 TMS coil, the functional circuit underlying these effects may engage inter-hemispheric reentrant mechanisms which have been implicated in visual recovery from stroke [10].

Our results provide behavioral evidence that neural plasticity induced by the function-tuning ccPAS protocol can be targeted on specific neural pathways, based on functionally selective mechanisms. When subthreshold TMS intensity is applied, only neurons tuned to the primed motion stimulus benefit from the strengthening of neural connections, giving rise to direction-selective induction of plasticity reflected in function-specific performance improvements. When high-intensity TMS is applied, the stimulation intensity is likely to be sufficient to activate neurons regardless of whether they have been activated by the visual stimulus. While this leads to generalized plasticity effects when ccPAS is applied at rest [3], lateral inhibition mechanisms in place during function-tuning ccPAS lead instead to no net behavioral plasticity.

Supplemental Information

Supplemental Information includes experimental procedures and two figures and can be found with this article online at *bxs.

Acknowledgments

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Authors contribution

J.S., A.A. and V.R. conceived the experiment. All the authors designed the experiment. E.C. performed the experiment and analysed the data. E.C., J.S. and V.R. wrote the first draft of the manuscript. All the authors contributed to the final version of the manuscript.

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[1]Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia, Università di Bologna, 47521, Cesena, Italy. [2]IRCCS Fondazione Santa Lucia, 00185 Rome, Italy. [3]Department of Psychology, Faculty of Science and Technology, University of Westminster, W1B 2HW London, UK. [4]Centre for Brain Science, Department of Psychology, University of Essex, Colchester, CO4 3SQ, UK. E-mail: vincenzo.romei@unibo.it

Figure 1. Function-tuning ccPAS, methods and results. (caption: before: 220w, now: 200w)

(A) Timeline of experiment. At the beginning of each session the PT was assessed for both V5/MT+ and V1/V2. PRE (before) and POST (30 min after ccPAS) blocks consisted of 600 trials each, with varying motion coherence (10 levels: 0-80%). Schematic trials: white and black arrows represent the motion direction of signal and noise dots respectively. The task consisted of a central fixation cross (500 ms) and a motion coherence stimulus (400 ms) presented in the right visual hemifield. During ccPAS, a motion stimulus (100% of coherence) was presented, but no response was required (Figure S1) (B) Results. Feature-specific facilitation induced by pairing visual stimulation (100% coherent motion) with ccPAS over V5/MT+ and V1/V2. Following ccPAS applied over V5/MT+ and then V1/V2 at 80% PT (eV5-V1_80), motion sensitivity was enhanced for the direction congruent (green bar) to that viewed during ccPAS; no effect was observed for the incongruent direction (red bar). No effects were observed when both sites were stimulated at PT (cV5-V1_100), or when V1/V2 TMS preceded V5/MT+ during ccPAS (cV1-V5_80). Modulation was effective for congruent but not the for the incongruent direction following eV5-V1_80 session only compared to each control session in the congruent direction (see Figure S2).

Supplemental Information

Document S1. Experimental Procedures and Two Figures.

In Brief

Utilising the Hebbian principle of synaptic plasticity, Chiappini *et al.* developed a protocol for selectively strengthening specific neural connections within the human V5-to-V1 pathway. State-

dependent TMS boosted visual sensitivity to specific motion directions, indicative of selective targeting of functionally specific neural pathways.