Clinical Neurophysiology 156 (2023) 290–292

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Letter to the Editor

Understanding the sources of cortico-cortical paired associative stimulation (ccPAS) variability: Unraveling target-specific and state-dependent influences

Cortico-cortical paired associative stimulation (ccPAS) is a powerful non-invasive brain stimulation technique that involves the repeated paired application of transcranial magnetic stimulation (TMS) to two different brain regions, with precise temporal intervals, to exogenously induce the phenomenon of spike timing-dependent plasticity and modulate the strength of connectivity between the targeted brain areas. In a recent systematic review published in *Clinical Neurophysiology*, Hernandez-Pavon and colleagues (Hernandez-Pavon et al., 2023) offer an excellent comprehensive synthesis of the literature on ccPAS, exhaustively summarizing findings on the application of ccPAS to multiple domains, reporting both neurophysiological and behavioral outcomes, and highlighting its potential in modulating brain connectivity. Although further second-level evidence is necessary, specifically in the form of meta-analyses to combine data from multiple studies and obtain a precise estimation of effect sizes, the systematic review raises intriguing topics of discussion.

In their review, the authors afford significant attention to studies that used ccPAS to modulate connectivity between two nodes of motor system, namely the ventral premotor (PMv) and primary motor (M1) cortices, which have been the target of the highest number of ccPAS studies, also very recently. These studies provide insights into the neurophysiological bases of the protocol, which may help us understand its functioning.

As the authors point out, ccPAS studies targeting PMv-M1 have produced some conflicting results: while the works of Buch et al. (2011) and Chiappini et al. (2020) suggest that applying ccPAS by pairing the activation of 'pre-synaptic' neurons in PMv with 'post-synaptic' neurons in M1 ($ccPAS_{PMv\rightarrow M1}$) increases inhibitory PMv → M1 interactions at rest, leading to long-term depression (LTD) effects, other studies point towards long-term potentiation (LTP) effects (Casarotto et al., 2023; Fiori et al., 2018; Turrini et al., 2022; 2023a, 2023b, 2023c). Hernandez-Pavon et al. argue that some of these findings could reflect state-dependent mechanisms: while $ccPAS_{PMv\rightarrow M1}$ effects at rest result in LTD, testing them during a grasping task results in LTP (Buch et al., 2011), aligning with paired-pulse evidence that the PMv → M1 pathway can shift from inhibitory to facilitatory modulations depending on its activation state (Davare et al., 2008).

Hernandez-Pavon et al. also propose that state-dependency could explain the observed LTP effects in Fiori et al.'s study (Fiori et al., 2018), reflected by an increase in motor excitability during a $ccPAS_{PMv\rightarrow M1}$ protocol administered following a grasping task, which would prime the PMv → M1 pathway and shift it to a facilitatory state, thus making the effects of $ccPAS_{PMv\rightarrow M1}$ excitatory. We note, however, that activation priming cannot explain LTP effects found during (Turrini et al., 2022) and following $ccPAS_{PMv\rightarrow M1}$ (Casarotto et al., 2023; Turrini et al., 2023c) when participants remained at rest. We thus raise attention to recent investigations, which clarified that LTP effects can be observed when the $ccPAS_{PMv\rightarrow M1}$ protocol repeatedly activates the excitatory PMv → M1 pathway (Turrini et al., 2023c), regardless of whether a priming motor task has been performed (Turrini et al., 2023a, 2023b) or not (Turrini et al., 2023c).

Indeed, excitatory PMv-M1 interactions can be observed at rest, too. Turrini et al. (2023c) used paired-pulse TMS with stimulation parameters similar to those used in prior $ccPAS_{PMv\rightarrow M1}$ studies reporting LTP (Casarotto et al., 2023; Fiori et al., 2018) (i.e., subthreshold conditioning of PMv at 90% of resting motor threshold, suprathreshold M1 stimulation, and an interstimulus interval of 6–8 ms) and found excitatory PMv → M1 interactions at rest. This may promptly explain the bidirectional effects found by ccPAS investigation of the PMv → M1 pathway: Buch et al. (2011) and Chiappini et al. (2020) adopted stimulation parameters known to recruit inhibitory cortico-cortical interactions (Davare et al., 2008; Fiori et al., 2016) and, consequently, found $ccPAS_{PMv\rightarrow M1}$ to strengthen the inhibitory conditioning effect of PMv stimulation over M1 excitability; on the other hand, other studies (Casarotto et al., 2023; Fiori et al., 2018; Turrini et al., 2022, 2023a, 2023b, 2023c) selected stimulation parameters found to recruit facilitatory cortico-cortical interactions (Turrini et al., 2023c) and, consistently, detected LTP effects following/during ccPAS.

Nonetheless, the issue of ccPAS state-dependent effects remains relevant but largely unexplored. Turrini et al. (2022) directly compared the LTP effects observed during $ccPAS_{PMv\rightarrow M1}$ when the protocol was administered immediately after motor tasks or following a rest period and found no differences, suggesting a lack of priming effects on ccPAS efficacy.

Beyond priming effects, TMS is influenced by the activation state of the underlying neural populations at the time of stimulation, and previous studies have established that ccPAS aftereffects are state-dependent in nature: Buch et al. applied ccPAS over PMv-M1 at rest and found increased inhibitory PMv-M1 interactions at rest and increased facilitation during a motor task (Buch et al., 2011), and Sel et al. reported that the same protocol affected oscillatory activity in distinct frequency bands depending on the trial type of a Go-NoGo task (Sel et al., 2021).

Conversely, to date, no studies have directly tackled whether manipulations of the brain state *during* ccPAS application, rather than in the subsequent testing phase, would lead to diverging, selective or enhanced aftereffects in the motor system. Previous results from a study targeting temporo-occipital areas during a

https://doi.org/10.1016/j.clinph.2023.08.019
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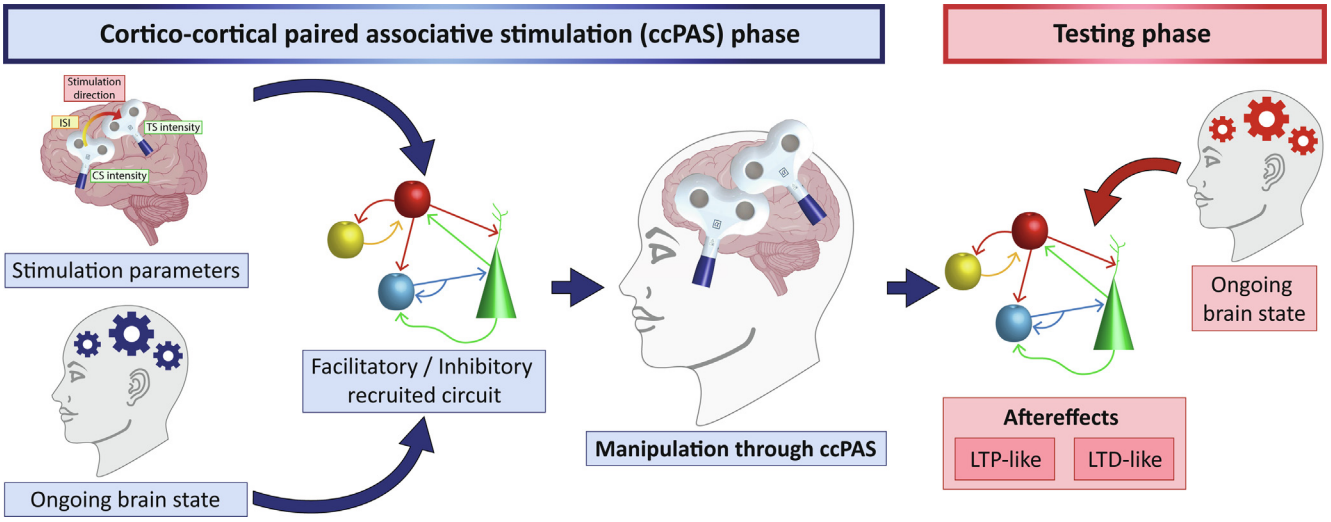

Fig. 1. Stimulation parameters and ongoing brain state can influence cortico-cortical pathways and cause a shift towards either excitation or inhibition in the circuit targeted by ccPAS. These factors can impact the ccPAS protocol during both the procedure and the testing phase.

visual task suggest that ccPAS aftereffects might reflect state-dependency (Chiappini et al., 2018). That work reported that ccPAS concurrently applied during the presentation of a specific motion direction led to remarkably selective aftereffects of improved perception of that exact visual feature only. Yet, whether this would hold true for the motor system or other domains remains an outstanding and yet unexplored research question.

Both research avenues are promising and worth exploring. Research should systematically evaluate how ccPAS can exert LTP/LTD influences depending on which excitatory/inhibitory circuits are optimally recruited and repeatedly activated during the protocol. This should be done across multiple cortico-cortical networks. Additionally, future work should clarify the conditions under which ccPAS directional effects depend on the activation state of the underlying neural population at the time of ccPAS administration (Fig. 1). It is likely that both target-specific and state-dependent effects play a role in determining ccPAS effects. Therefore, careful consideration of both stimulation parameter selection and brain state could provide a deeper understanding of the physiological bases of ccPAS. More second level evidence, such as the important work of Hernandez-Pavon and colleagues, will be essential for this endeavor.

Funding

Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

Alessio Avenanti is also supported by FISM – Fondazione Italiana Sclerosi Multipla (2022/R-Single/071) financed or cofinanced with the '5 per mille' public funding, and by grants from the Bial Foundation (304/2022), Fondazione del Monte di Bologna e Ravenna (1402bis/2021), Universidad Católica Del Maule (CDPDS2022).

Declaration of interest

None.

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Sonia Turrini *
Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia "Renzo Canestrari", Alma Mater Studiorum Università di Bologna, Cesena Campus, 47521 Cesena, Italy
* Corresponding author.
E-mail address: sonia.turrini3@unibo.it

Alessio Avenanti **
Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia "Renzo Canestrari", Alma Mater Studiorum Università di Bologna, Cesena Campus, 47521 Cesena, Italy
Centro de Investigación en Neuropsicología y Neurociencias Cognitivas (CINPSI Neurocog), Universidad Católica Del Maule, 346000 Talca, Chile
** Corresponding author.
E-mail addresses: alessio.avenanti@unibo.it
Accepted 2 August 2023

Available online 27 September 2023