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Cortico-cortical paired-associative stimulation to investigate the plasticity of cortico-cortical visual networks in humans☆

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Cortico-cortical paired-associative stimulation (ccPAS) is an advanced dual-site transcranial magnetic stimulation technique that exploits the Hebbian principle to induce plastic changes in functional networks and modulate interactions between cortical brain regions. This review summarizes the growing body of ccPAS research on network dynamics underpinning visual perception. Studies revealed a functional dissociation within cortico-cortical connections in the visual system, where distinct hierarchically organized circuits shape diverse aspects of visual processing, including motion perception, emotion recognition, and metacognitive judgments. Prospective applications integrating ccPAS with neuroimaging techniques such as EEG/MEG hold promise for fine-tuning interventions and gaining deeper insights into visual system network dynamics and functional architecture, with potential clinical applications in neurological and psychiatric conditions.

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Introduction

The emergence of advanced noninvasive brain stimulation (NIBS) techniques has prompted a transformative shift in cognitive neuroscience, leading to the development of novel conceptual frameworks and practical applications. Transcranial magnetic stimulation (TMS) has gained considerable recognition among NIBS methodologies due to its high adaptability and safety in modulating brain activity [1–3]. Studies have used TMS to perturb specific cortical regions and test their critical role in behavior, demonstrating, for example, that V5 plays a key role in the perception of visual motion [4], the occipital face area and extrastriate body area are important for perceiving morphological aspects of faces and bodies [5,6], and the posterior temporal sulcus (pSTS) is crucial for recognition of biological motion [7], actions [8], and emotional expressions [9,10]. These findings highlight the specific contributions of distinct portions of temporo-occipital areas to visual perception and provide valuable insights into the neural mechanisms underlying the processing of different stimulus categories.

Building upon early interferential studies, further TMS techniques have been developed for examining the functional interactions between interconnected cortical areas, primarily in the motor system. These techniques, known as paired-pulse TMS, enable the investigation of time-resolved effective connectivity by delivering two TMS pulses at varying interstimulus intervals (ISIs) over two cortical areas using two coils [11–13], the underlying rationale that, if the two are functionally connected, the impact of the second pulse is modulated by the first pulse.

In the motor system, the technique is implemented by delivering a test stimulus (TS) to the primary motor cortex (M1) to record motor-evoked potentials (MEPs) in peripheral muscles and assess motor excitability. To study the effective connectivity between M1 and a remote functionally connected cortical site, in some trials, the TS is preceded by a conditioning stimulus (CS) delivered to the remote site through another coil. The strength of the connectivity can be measured by how

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much the CS affects M1 excitability, as reflected in the amplitude of the MEPs evoked by M1 stimulation alone or paired-pulse stimulation. Critically, the timing of the connectivity can be precisely mapped by systematically probing the ISI between the CS and TS at several different values [11,14–16]. The same ppTMS approach has been applied to the visual system, too, delivering the TS over V1 paired with CS over V5 and examining the modulation of moving phosphene perception depending on the ISI between TS and CS, to establishing the timing of effective V5–V1 connectivity [17,18].

Stemming from this instrumental knowledge on the timing of effective connectivity in select pathways that can be exogenously stimulated through TMS, it is possible to act on plastic mechanisms both to strengthen and weaken the influence that one area has on the other by repeatedly applying pairs of TMS pulses [19–23].

Such a procedure is referred to as cortico-cortical paired-associative stimulation (ccPAS) [21,24–28] and has been first developed by Rizzo and colleagues [29]. Crucially, the effectiveness of ccPAS in inducing long-lasting plastic changes is contingent on the precise timing of the TMS pulses, pointing to the involvement of an underlying Hebbian-like mechanism. According to the Hebbian rule [30], synapses are potentiated when presynaptic neurons repeatedly and consistently fire immediately before postsynaptic neurons. The ccPAS protocol exogenously mimics this principle by activating pre- and postsynaptic neurons with a temporally precise pattern to induce Hebbian-like spike-timing-dependent plasticity (STDP) [30,31]. For example, Buch and colleagues demonstrated that ccPAS applied over the ventral premotor cortex (PMv) and M1, with an 8-ms ISI, tailored to the temporal properties of the PMv-to-M1 pathway revealed by ppTMS studies [32,33], increases the conditioning effect exerted by PMv over M1. Specifically, the authors showed that the application of the first pulse of TMS on PMv (regarded as the 'presynaptic' node according to the Hebbian rule) may preactivate via cortico-cortical connections, M1 (the 'postsynaptic' node) shortly before the application of the second pulse on M1. This pre- and postsynaptic activation coupling is optimal for inducing STDP, increasing synaptic plasticity and connectivity in the pathway between the premotor and motor regions.

These findings demonstrated that ccPAS can increase the synaptic efficacy of cortical projections from the first to the second targeted area, showing long-term potentiation (LTP)-like effects [34,35]. Moreover, by reversing the order of the stimulation pairs, a connection weakening can be achieved, resulting in long-term depression (LTD) [34,36]. Subsequent studies have combined ccPAS with imaging and/or electrophysiological techniques to elucidate the timing of insurgence of plastic effects during protocol administration [36], provide network-level evidence of anatomically specific increased cortico-cortical functional coupling [22,37–39], clarify the engagement of specific excitatory and inhibitory intracortical networks [40,41], and demonstrate functionally specific behavioral effects [42–44]. Although these Hebbian-like plasticity chances were first documented in the motor control network, changes in cortico-cortical plasticity with ccPAS are also extensively observed in the visual network. In this short review, we will summarize and comment on the body of work dedicated to examining the cortico-cortical connections supporting visual perception and how they relate to the visual perceptual abilities that they underpin.

In the figure, we have offered a graphical overview of the key visual networks explored through the ccPAS protocol to date. These networks involve a complex interplay within the visual cortex, revealing a dynamic process crucial for visual information processing. Notably, the V5–V1 network plays a pivotal role in integrative visual functions essential for motion awareness. Specifically, suppressing V5 weakens V1 responses to moving bar stimuli, and subthreshold TMS stimulation on V5 can elicit moving phosphenes when suprathreshold V1 stimulation follows, suggesting a top-down amplification mechanism in visual motion processing subserved by V5-to-V1 network [17,18]. Moreover, motion awareness is also critically linked to the interplay of the horizontal interaction between the homologous V5 areas in both hemispheres via callosal connections. This connection is noteworthy, as the strength of connectivity in the V5–V5 pathway is directly correlated with heightened horizontal motion sensitivity [45]. Advancing to higher-order areas, the intraparietal sulcus (IPS) plays a pivotal role in perceptual decision-making [46] and decisional confidence [47,48]. Importantly, ample evidence suggests a close anatomo-functional relationship between IPS and occipital regions [50], contributing to the top-down regulation of primary visual areas through the feedback information flow it provides [51]. Finally, the superior temporal sulcus (STS)–V1 network stands out for its involvement in social perception and biological motion processing. STS plays a crucial role in recognizing facial expressions, processing biological motion cues, and extracting socially relevant information from visual stimuli. Face-selective neurons of pSTS receive projections directly from the periphery of V1/V2, and in turn, pSTS sends direct and indirect back-projections to V1/V2. Consistent with these reciprocal connections, pSTS and V1/V2 exhibit intrinsic functional connectivity at rest, predicting interindividual differences in emotion recognition accuracy.

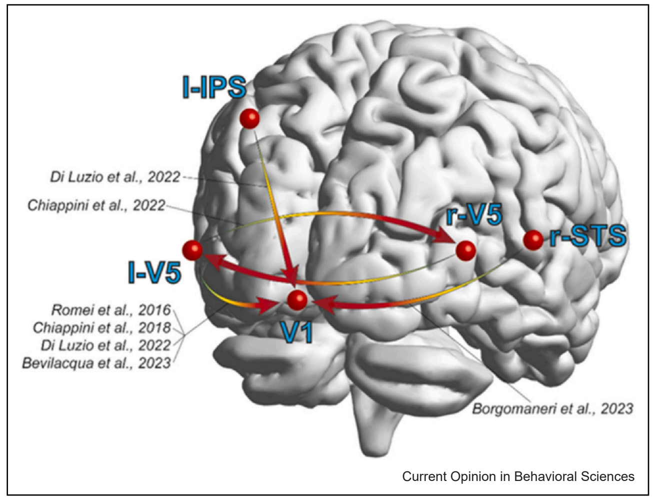
Investigating plasticity in visual networks through cortico-cortical paired-associative stimulation

Recent research has extended ccPAS applications to investigate the plasticity of cortico-cortical visual networks (Figure 1). The first notable application, conducted by Romei et al. [21], explored the plasticity of the left V5–V1 network and its role in visual motion discrimination. The study demonstrated that the ccPAS protocol specifically designed to strengthen the reentrant left V5-to-V1 pathway led to significant improvements in motion discrimination when the directionality and timing of the ccPAS protocol aligned with the temporal properties of the stimulated pathway. The observed effects showed a long-lasting temporal unfolding, resembling Hebbian-like physiological changes obtained in previous studies on the motor system. Conversely, no net modulation in motion discrimination performance was achieved when the TMS protocol did not closely mimic the intrinsic spatiotemporal dynamics of the stimulated network.

In addition to complying with the temporal rules governing the interaction within the circuits, the expression of plastic mechanisms could also be influenced by the network's activation state. For instance, it is well-recognized that the effect of NIBS can be potentiated or attenuated based on the prevailing level of neural excitation at the site of application [51,52]. In light of this principle, Chiappini et al. [53] evaluated whether the effect of ccPAS on the left V5–V1 pathway could be influenced by the current state of excitation of the stimulated brain network. The researchers demonstrated that when ccPAS pulses were delivered during the concurrent presentation of a specific motion direction, motion sensitivity increased only for that specific motion direction. This finding highlights the potential for state-dependent ccPAS to facilitate precise targeting of specific functional circuits within overlapping pathways, thereby enhancing the spatial and functional specificity of ccPAS.

Collectively, these findings have linked the V5–V1 network to establishing the precision with which motion-based information is sampled. Recently, this picture has been further expanded by a study conducted by Di Luzio et al. [54] that revealed the causal involvement of

Figure 1



Overview of the functional role of visual networks investigated with ccPAS.

the left IPS–V1 network in determining the accuracy of metacognitive judgments on perceptual decisions. Specifically, the ccPAS protocol targeting the reentrant connections from left IPS to V1 selectively influenced metacognitive capacity, enabling participants to exhibit greater precision in estimating the correctness of their choices without affecting the actual accuracy of perceptual decision-making. On the other hand, while left V5-to-V1 ccPAS resulted in improvements in perceptual performance, it did not yield any changes in the participants' metacognitive judgments.

In summary, these ccPAS studies provide valuable insights into the role of different cortico-cortical connections within the visual network, shedding light on the selective modulation of perceptual sensitivity by V5-to-V1 back-projections and metacognitive efficiency by IPS-to-V1 back-projections. These findings support the existence of distinct and hierarchical networks that govern human perceptual decision-making processes.

However, the hierarchical organization of the perceptual domain encompasses not only vertical chains that ascend the visual system in a sequential manner (bottom-up and top-down) but also involves horizontal pathways that emerge through the interaction between homologous areas of the two hemispheres via callosal connections. A recent ccPAS study by Chiappini, Sel et al. [55] has characterized these horizontal interactions, revealing functional dissociations between interhemispheric networks. Using an optimized ccPAS protocol, the authors specifically enhanced the connectivity between the V5 regions of the left and right hemispheres in a series of five consecutive experiments. The results demonstrated a functional dissociation, as reinforcing the left-to-right V5 pathway heightened sensitivity to horizontal visual motion, while strengthening the right-to-left V5 pathway did not produce the same effect. These findings provide compelling evidence supporting the functional relevance and asymmetrical plasticity of interhemispheric projections between the left and right V5 regions to horizontal motion perception. It is worth emphasizing that this conceptual progress made possible by ccPAS, which allowed researchers to disentangle the dissociable functional role of V5–V1 and IPS–V1 reentrant projections and highlight the functional asymmetries observed in interhemispheric interactions, would have presented challenges to dissect with comparable precision using conventional neurostimulation approaches.

Finally, in a recent study conducted by Borgomaneri et al. [56], the researchers aimed to enhance the visual perception of facial expressions by targeting long-range projections between right pSTS and V1. They combined TMS and electroencephalography (EEG) to track signal propagation from right pSTS to V1, estimate its timing, and inform a subsequent pSTS–V1 ccPAS: single-pulse TMS was initially delivered over the right pSTS, and the time-course of TMS-evoked responses within V1 was recorded. STS stimulation induced a maximal EEG peak over V1 ~200 ms after the pulse, consistent with the recruitment of long-range and polysynaptic reentrant temporo-occipital connections. This information was then used to calibrate a ccPAS of the two regions, with the hypothesis that reinforcing communication from pSTS to V1 would improve the recognition of emotional facial expressions. The study's results demonstrated that right pSTS-to-V1 ccPAS improved the ability to recognize emotions from facial stimuli, leaving gender perception unaffected, accompanied by increased EEG activity in both pSTS and V1. These findings highlight the potential of ccPAS not only to modulate the perception of simple motion stimuli but also to influence the processing of complex and biologically relevant stimuli, such as emotional faces, which are typically associated with the ventral visual system.

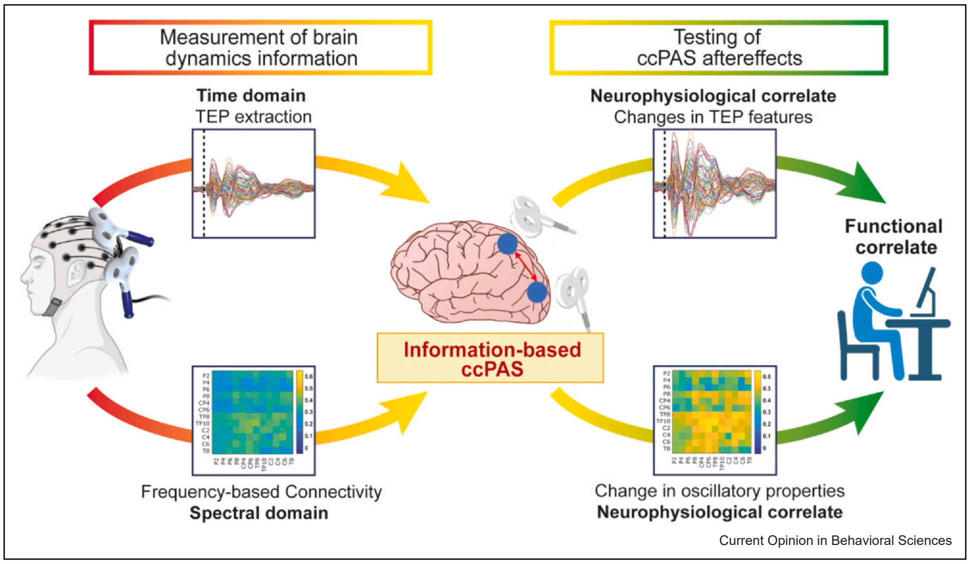
Future directions and clinical implications

Further research efforts are needed to explore the full potential of ccPAS in investigating the plasticity of cortico-cortical networks. One of the main objectives for future studies is to further integrate ccPAS with neuroimaging techniques [22,25,26,35,39] to gain a mechanistic understanding of the impact exerted by cortico-cortical plasticity on human behavior. In line with this objective, a recent study [57] has investigated the neural correlates of the improvement in motion discrimination tasks following V5-to-V1 ccPAS. The research revealed that the enhancement in motion direction discrimination was linked to increased effective top-down connectivity from V5 to V1 in the alpha band. Moreover, Borgomaneri et al. [56] demonstrated that improved emotion perception following pSTS–V1 ccPAS was paralleled by an increase in the temporo-occipital activity induced by facial stimuli, with maximal effects over V1, suggesting increased top-down modulation from pSTS to V1. These findings provide proof-of-principle evidence that ccPAS can effectively modulate the strength of top-down reentrant visual networks, with corresponding cascading effects on the behavioral output of visual circuits, and contribute to our understanding of the neurophysiological rules governing network dynamics. This comprehension is crucial for fine-tuning ccPAS protocols and maximizing the effectiveness of the interventions.

To this endeavor, future information-based ccPAS approaches should take into consideration spatiotemporal properties of the targeted network as gathered from EEG signals such as TMS-evoked potentials (TEP) [56] or the rhythmic nature of the interactions between cerebral networks (Figure 2) [39,58]. Consequently, prospective research could focus on developing information-based approaches [47], such as TEP-based or rhythmic-based ccPAS protocols, by adjusting the delay between the two TMS pulses to correspond to a specific TEP component or in order to accurately mimic the intrinsic rhythmic interaction that occurs in cortico-cortical interactions.

These innovative approaches are currently being implemented in our labs, where we are exploring the intriguing possibility of tailoring ccPAS protocols to specific EEG frequencies to selectively enhance brain connectivity in specific brain networks. In this regard, mounting evidence suggests that different frequency features and bands are implicated in distinct cognitive functions [47–51,59–62], further supporting the notion that frequency-specific strengthening of the same network may elicit diverse behavioral outcomes with significant implications. Among these, information-based ccPAS protocols may yield substantial advances in the current understanding of how the ccPAS operates, helping to disentangle the complexity and variability of the results currently available. The growing interest in paired-associative stimulation protocols has resulted in an increase in publications on the topic [63], revealing both the remarkable efficacy of this tool and, on the other, thought-provoking discrepancies in findings whose root causes are yet to be defined [64]. In pursuit of this, the use of information-based ccPAS methods, along with their application in animal models to study how the ccPAS activates STDP, could prove pivotal, advocating for further studies to enhance our comprehension of ccPAS mechanisms and contribute to the resolution of existing discrepancies.

Figure 2



Prospective EEG-informed ccPAS protocols in the visual system. Information-based ccPAS approaches take into consideration the spatiotemporal properties of the targeted network. This information can be obtained from EEG/magnetoencephalography (MEG) signals in combination with TMS or as standalone techniques, which can trace the interaction between brain regions with high temporal resolution. As a result, research in this field is currently focused on two main prospective directions: i) TEP-based ccPAS protocols that involve adjusting the delay between the two TMS pulses corresponding to a specific TEP component. This precise targeting of EEG-derived components can potentially enhance cortico-cortical plasticity more effectively. II) Rhythmic-based ccPAS protocols that tailor the delay between TMS pulses to mimic the intrinsic rhythmic interactions observed in cortico-cortical circuits accurately. By aligning with these natural rhythms, the protocol can facilitate the expression of plasticity in a frequency-specific manner. Overall, by exploring and fine-tuning these approaches, researchers can unlock the full potential of ccPAS to modulate neuroplasticity.

Understanding the plasticity of cortico-cortical networks through ccPAS has also significant translational implications. Initial steps in this direction have explored the impact of ccPAS on psychiatric [65,66] as well as neurological [67] populations. These seminal works indicate that ccPAS could pave the way for targeted interventions in clinical conditions characterized by motor [68] or visuospatial deficits [69], such as hemianopia, neglect, or agnosia. Furthermore, several symptoms observed in psychiatric populations, such as autism and schizophrenia spectrum disorders, often visual in nature, could stem from imbalanced connections between cerebral hubs [70–73], and cortical imbalance can characterize several other conditions, including migraine [74]. Therefore, both established and novel information-based ccPAS protocols may serve as promising candidates for potential therapeutic interventions, as they could provide highly specific and individually tailored approaches to modulate neural connectivity.

CRediT authorship contribution statement

Luca Tarasi: Investigation; Visualization; roles/Writing – original draft. **Sonia Turrini**: Investigation; Visualization; roles/Writing – original draft. **Alejandra Sel**: Conceptualization; Funding acquisition; Resources; Supervision; Writing – review & editing. **Alessio Avenanti**: Conceptualization; Funding acquisition; Resources; Supervision; Writing – review & editing. **Vincenzo Romei**: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

None.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, Carpenter LL, Cincotta M, Chen R, Daskalakis JD, *et al.*: **Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert Guidelines**. *Clin Neurophysiol* 2021, **132**:269-306.

2. Pitcher D, Parkin B, Walsh V: **Transcranial magnetic stimulation and the understanding of behavior**. *Annu Rev Psychol* 2021, **72**:97-121.

3. Hartwigsen G, Silvanto J: **Noninvasive brain stimulation: multiple effects on cognition**. *Neuroscientist* 2022, **29**:639-653, https://doi.org/10.1177/10738584221113806

4. Walsh V, Ellison A, Battelli L, Cowey A: **Task–specific impairments and enhancements induced by magnetic stimulation of human visual area V5**. *Proc R Soc Lond Ser B Biol Sci* 1998, **265**:537-543.

5. Urgesi C, Candidi M, Ionta S, Aglioti SM: **Representation of body identity and body actions in extrastriate body area and ventral premotor cortex**. *Nat Neurosci* 2007, **10**:30-31.

6. Pitcher D, Charles L, Devlin JT, Walsh V, Duchaine B: **Triple dissociation of faces, bodies, and objects in extrastriate cortex**. *Curr Biol* 2009, **19**:319-324.

7. Grossman ED, Battelli L, Pascual-Leone A: **Repetitive TMS over posterior STS disrupts perception of biological motion**. *Vis Res* 2005, **45**:2847-2853.

8. Cattaneo L, Sandrini M, Schwarzbach J: **State-dependent TMS reveals a hierarchical representation of observed acts in the temporal, parietal, and premotor cortices**. *Cereb Cortex* 2010, **20**:2252-2258.

9. Pitcher D: **Facial expression recognition takes longer in the posterior superior temporal sulcus than in the occipital face area**. *J Neurosci* 2014, **34**:9173-9177.

10. Paracampo R, Pirruccio M, Costa M, Borgomaneri S, Avenanti A: **Visual, sensorimotor and cognitive routes to understanding others' enjoyment: an individual differences rTMS approach to empathic accuracy**. *Neuropsychologia* 2018, **116**:86-98.

11. Hallett M, Di Iorio R, Rossini PM, Park JE, Chen R, Celnik P, Strafella AP, Matsumoto H, Ugawa Y: **Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks**. *Clin Neurophysiol* 2017, **128**:2125-2139.

12. Koch G: **Cortico-cortical connectivity: the road from basic neurophysiological interactions to therapeutic applications**. *Exp Brain Res* 2020, **238**:1677-1684.

13. Lafleur L-P, Tremblay S, Whittingstall K, Lepage J-F: **Assessment of effective connectivity and plasticity with dual-coil transcranial magnetic stimulation**. *Brain Stimul Basic Transl Clin Res Neuromodulation* 2016, **9**:347-355.

14. Davare M, Lemon R, Olivier E: **Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans**. *J Physiol* 2008, **586**:2735-2742.

15. Koch G, Ruge D, Cheeran B, Fernandez Del Olmo M, Pecchioli C, Marconi B, Versace V, Lo Gerfo E, Torriero S, Oliveri M, *et al.*: **TMS activation of interhemispheric pathways between the posterior parietal cortex and the contralateral motor cortex**. *J Physiol* 2009, **587**:4281-4292.

16. Reis J, Swayne O, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, Perez MA, Ragert P, Rothwell JC, Cohen LG: **Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control**. *J Physiol* 2008, **586**:325-351.

17. Pascual-Leone A, Walsh V: **Fast backprojections from the motion to the primary visual area necessary for visual awareness**. *Science* 2001, **292**:510-512.

18. Silvanto J, Lavie N, Walsh V: **Double dissociation of V1 and V5/MT activity in visual awareness**. *Cereb Cortex* 2005, **15**:1736-1741.

19. Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MFS: **Noninvasive associative plasticity induction in a corticocortical pathway of the human brain**. *J Neurosci* 2011, **31**:17669-17679.

20. Koch G, Ponzo V, Lorenzo FD, Caltagirone C, Veniero D: **Hebbian and anti-hebbian spike-timing-dependent plasticity of human cortico-cortical connections**. *J Neurosci* 2013, **33**:9725-9733.

21. Romei V, Chiappini E, Hibbard PB, Avenanti A: **Empowering reentrant projections from V5 to V1 boosts sensitivity to motion**. *Curr Biol* 2016, **26**:2155-2160.

22. Sel A, Verhagen L, Angerer K, David R, Klein-Flügge MC, Rushworth MFS: **Increasing and decreasing interregional brain coupling increases and decreases oscillatory activity in the human brain**. *Proc Natl Acad Sci* 2021, **118**:e2100652118.

23. Turrini S, Fiori F, Chiappini E, Lucero B, Santarnecchi E, Avenanti A: **Cortico-cortical paired associative stimulation (ccPAS) over premotor-motor areas affects local circuitries in the human motor cortex via Hebbian plasticity**. *NeuroImage* 2023, **271**:120027.

24. •• Cesar Hernandez-Pavon J, San Agustín A, Wang MC, Veniero D, Pons JL: **Can we manipulate brain connectivity? A systematic review of cortico-cortical paired associative stimulation effects**. *Clin Neurophysiol* 2023, **154**:169-193, https://doi.org/10.1016/j.clinph.2023.06.016.

This is the first systematic review on the use of ccPAS, specifically looking at its physiological and behavioral effects across different neural networks, including motor and visual pathways.

25. Koch G, Ponzo V, Lorenzo FD, Caltagirone C, Veniero D: **Hebbian and anti-hebbian spike-timing-dependent plasticity of human cortico-cortical connections**. *J Neurosci* 2013, **33**:9725-9733.

26. Veniero D, Ponzo V, Koch G: **Paired associative stimulation enforces the communication between interconnected areas**. *J Neurosci* 2013, **33**:13773-13783.

27. Zibman S, Daniel E, Alyagon U, Etkin A, Zangen A: **Interhemispheric cortico-cortical paired associative stimulation of the prefrontal cortex jointly modulates frontal asymmetry and emotional reactivity**. *Brain Stimul* 2019, **12**:139-147.

28. Momi D, Neri F, Coiro G, Smeralda C, Veniero D, G S, A R, A P-L, S R, E S: **Cognitive enhancement via network-targeted cortico-cortical associative brain stimulation**. *Cereb Cortex* 2020, **30**:1516-1527.

29. Rizzo V, Siebner HS, Morgante F, Mastroeni C, Girlanda P, Quartarone A: **Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a hebbian mechanism**. *Cereb Cortex* 2009, **19**:907-915.

30. Caporale N, Dan Y: **Spike timing-dependent plasticity: a Hebbian learning rule**. *Annu Rev Neurosci* 2008, **31**:25-46.

31. Markram H, Gerstner W, Sjöström PJ: **A history of spike-timing-dependent plasticity**. *Front Synaptic Neurosci* 2011, **3**:4.

32. Davare M, Lemon R, Olivier E: **Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans**. *J Physiol* 2008, **586**:2735-2742.

33. Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN: **Ventral premotor to primary motor cortical interactions during object-driven grasp in humans**. *Cortex* 2009, **45**:1050-1057.

34. Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MFS: **Noninvasive associative plasticity induction in a corticocortical pathway of the human brain**. *J Neurosci* 2011, **31**:17669-17679.

35. Santarnecchi E, Momi D, Sprugnoli G, Neri F, Pascual-Leone A, Rossi A, Rossi S: **Modulation of network-to-network**

connectivity via spike-timing-dependent noninvasive brain stimulation. *Hum Brain Mapp* 2018, **39**:4870-4883.

36. • Turrini S, Fiori F, Chiappini E, Santarnecchi E, Romei V, Avenanti A: **Gradual enhancement of corticomotor excitability during cortico-cortical paired associative stimulation**. *Sci Rep* 2022, **12**:14670.
This study investigates the online effects of ccPAS over the PMv-to-M1 circuit by monitoring MEPs during protocol administration. Authors observed a progressive increase in corticomotor excitability, reflecting the gradual build-up of plasticity during PMv-to-M1 ccPAS. The reverse M1-to-PMv ccPAS protocol was instead accompanied by an inhibitory trend.

37. Johnen VM, Neubert F-X, Buch ER, Verhagen L, O'Reilly JX, Mars RB, Rushworth MFS: **Causal manipulation of functional connectivity in a specific neural pathway during behaviour and at rest**. *eLife* 2015, **4**:e04585.

38. Chiappini E, Borgomaneri S, Marangon M, Turrini S, Romei V, Avenanti A: **Driving associative plasticity in premotor-motor connections through a novel paired associative stimulation based on long-latency cortico-cortical interactions**. *Brain Stimul* 2020, **13**:1461-1463.

39. • Trajkovic J, Romei V, Rushworth MFS, Sel A: **Changing connectivity between premotor and motor cortex changes inter-areal communication in the human brain**. *Prog Neurobiol* 2023, **228**:102487.
This study explored the relationship between the PMv and the M1 using ccPAS. The researchers found that ccPAS induced changes in PMv-M1 phase synchrony, leading to increased alpha and beta band synchrony after ccPAS PMv-to-M1 stimulation and decreased theta phase synchrony after ccPAS M1-to-PMv stimulation. The study sheds light on the connection between the motor network's physiology and its interactions mediated by specific resonant frequencies, providing insights into the relationship between synaptic efficacy and brain oscillations.

40. • Casarotto A, Dolfini E, Cardellicchio P, Fadiga L, D'Ausilio A, Koch G: **Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network**. *J Physiol* 2023, **601**:211-226.
This study assessed the physiological modifications produced by Hebbian-like plasticity in the PMv-M1 network. Following PMv-M1 ccPAS, corticospinal excitability negatively correlates with I_2-wave amplitude, consistent with the notion that this wave is modulated by the induction of plasticity in this network. Importantly, different ccPAS coil orientations were associated with opposite plasticity effects, leading to LTP or LTD-like effects in M1.

41. • Turrini S, Fiori F, Chiappini E, Lucero B, Santarnecchi E, Avenanti A: **Cortico-cortical paired associative stimulation (ccPAS) over premotor-motor areas affects local circuitries in the human motor cortex via Hebbian plasticity**. *Neuroimage* 2023, **271**:120027.
This study combined single-pulse, paired-pulse and dual-site TMS to show that when ccPAS is used to repeatedly stimulate excitatory circuits from PMv to M1, it leads to local LTP effects. The study also found a decrease in GABAergic transmission in M1 after an excitatory ccPAS, suggesting that the protocol can affect the balance between excitation and inhibition.

42. Fiori F, Chiappini E, Avenanti A: **Enhanced action performance following TMS manipulation of associative plasticity in ventral premotor-motor pathway**. *Neuroimage* 2018, **183**:847-858.

43. • Turrini S, Bevacqua N, Cataneo A, Chiappini E, Fiori F, Battaglia S, Romei V, Avenanti A: **Neurophysiological markers of premotor–motor network plasticity predict motor performance in young and older adults**. *Biomedicines* 2023, **11**:1464.
In this study, researchers used the induction of MEP increase induced by ccPAS over the PMv-M1 pathway as a proxy of the plastic potential of the circuit in healthy elderly adults. They observed a correlation between this metric and the baseline behavioral output of the same premotor-motor network. The study highlights the potential for ccPAS to be a tool to study plasticity in the young and elderly brain, and to elucidate the contribution of plasticity to the maintenance of brain health.

44. • Turrini S, Bevacqua N, Cataneo A, Chiappini E, Fiori F, Candidi M, Avenanti A: **Transcranial cortico-cortical paired associative stimulation (ccPAS) over ventral premotor-motor pathways enhances action performance and corticomotor excitability in young adults more than in elderly adults**. *Front Aging Neurosci* 2023, **15**:1119508.
This study compared the effectiveness of ccPAS between young and elderly individuals. It was reported that ccPAS over PMv-M1 enhanced motor dexterity and corticomotor excitability in young individuals, but not older individuals as a group. Interestingly, the two effects were correlated in both groups, indicating that older individuals who had neurophysiological response to ccPAS, also showed improved motor functions.

45. Genç E, Bergmann J, Singer W, Kohler A: **Interhemispheric connections shape subjective experience of bistable motion**. *Curr Biol* 2011, **21**:1494-1499.

46. Gold JI, Shadlen MN: **The neural basis of decision making**. *Annu Rev Neurosci* 2007, **30**:535-574.

47. Gherman S, Philiastides MG: **Neural representations of confidence emerge from the process of decision formation during perceptual choices**. *NeuroImage* 2015, **106**:134-143.

48. Kiani R, Shadlen MN: **Representation of confidence associated with a decision by neurons in the parietal cortex**. *Science* 2009, **324**:759-764.

49. Caspers S, Zilles K: **Microarchitecture and connectivity of the parietal lobe**. *Handb Clin Neurol* 2018, **151**:53-72.

50. Tarasi L, di Pellegrino G, Romei V: **Are you an empiricist or a believer? Neural signatures of predictive strategies in humans**. *Prog Neurobiol* 2022, **219**:102367.

51. Silvanto J, Muggleton NG, Cowey A, Walsh V: **Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation**. *Eur J Neurosci* 2007, **25**:1874-1881.

52. Silvanto J, Pascual-Leone A: **State-dependency of transcranial magnetic stimulation**. *Brain Topogr* 2008, **21**:1-10.

53. Chiappini E, Silvanto J, Hibbard PB, Avenanti A, Romei V: **Strengthening functionally specific neural pathways with transcranial brain stimulation**. *Curr Biol* 2018, **28**:R735-R736.

54. •• Luzio PD, Tarasi L, Silvanto J, Avenanti A, Romei V: **Human perceptual and metacognitive decision-making rely on distinct brain networks**. *PLoS Biol* 2022, **20**:e3001750.
In this study, researchers used ccPAS to induce changes in specific brain networks and investigated the relationship between perceptual sensitivity and metacognitive ability in decision-making. They found separate neural pathways for each cognitive process (i.e. IPS-V1 mediate metacognition; V5-V1 mediate visual sensitivity), revealing distinct networks responsible for perceptual sensitivity and metacognitive efficiency.

55. •• Chiappini E, Sel A, Hibbard PB, Avenanti A, Romei V: **Increasing interhemispheric connectivity between human visual motion areas uncovers asymmetric sensitivity to horizontal motion**. *Curr Biol* 2022, **32**:4064-4070 e3.
First ccPAS study on the investigation of interhemispheric connections in the visual system. By stimulating V5 to V5 connections, researchers found a preferential functional effect for left-to-right directionality for interhemispheric apparent motion perception, suggesting a functional asymmetry in motion perception for integrating sensory input into coherent motion perception.

56. •• Borgomaneri S, Zanon M, Di Luzio P, Cataneo A, Arcara G, Tamietto M, Avenanti A: **Increasing associative plasticity in temporo-occipital back-projections improves visual perception of emotions from facial stimuli**. *Nat Commun* 2023, **14**:5720.
This is the first study using TEP to inform precise timing of the ccPAS protocol. The timing corresponding to the second peak of the TEP of 200ms has been used to improve visual perception of emotions from facial stimuli by inducing plasticity in temporo-occipital back-projections.

57. •• Bevilacqua M, Huxlin KR, Hummel FC, Raffin E: **Pathway and directional specificity of Hebbian plasticity in the cortical visual motion processing network**. *iScience* 2023, **26**:107064.
This study replicates behavioral findings from Romei et al., 2016 and Chiappini et al., 2018 showing that enhancing connectivity between V5 and V1 facilitates coherent motion perception. Importantly, by recording EEG, they report a significant change in oscillatory alpha activity following V5-to-V1 but not V1 to-V5 stimulations, supporting a role for this frequency band in controlling back-projections connectivity and related functions.

58. Fries P: **Rhythms for cognition: communication through coherence**. *Neuron* 2015, **88**:220-235.

59. Di Gregorio F, Trajkovic J, Roperti C, Marcantoni E, Di Luzio P, Avenanti A, Thut G, Romei V: **Tuning alpha rhythms to shape conscious visual perception**. *Curr Biol* 2022, **32**:988-998, https://doi.org/10.1016/j.cub.2022.01.003 e6.

60. Tarasi L, Trajkovic J, Diciotti S, di Pellegrino G, Ferri F, Ursino M, Romei V: **Predictive waves in the autism-schizophrenia continuum: a novel biobehavioral model**. *Neurosci Biobehav Rev* 2022, **132**:1-22.

61. Tarasi L, Romei V: **Individual alpha frequency contributes to the precision of human visual processing**. *J Cogn Neurosci* 2023, **25**:1-11.

62. Trajkovic J, Gregorio FD, Avenanti A, Thut G, Romei V: **Two oscillatory correlates of attention control in the alpha-band with distinct consequences on perceptual gain and metacognition**. *J Neurosci* 2023, **43**:3548-3556.

63. Hernandez-Pavon JC, San Agustín A, Wang MC, Veniero D, Pons JL: **Can we manipulate brain connectivity? A systematic review of cortico-cortical paired associative stimulation effects**. *Clin Neurophysiol* 2023, **154**:169-193, https://doi.org/10.1016/j.clinph.2023.06.016

64. Turrini S, Avenanti A: **Understanding the sources of cortico-cortical paired associative stimulation (ccPAS) variability: unraveling target-specific and state-dependent influences**. *Clin Neurophysiol* 2023, **156**:293-294.

65. Lin Y, Chen P, Yang K, Zhou Q, Zhan S, Lin H, Li L, Wang L, Wang Y: **Efficacy of repetitive dual-site paired associative Transcranial magnetic stimulation in the treatment of generalized anxiety disorder**. *Brain Stimul* 2020, **13**:1170-1172.

66. Wang J, Wang X, Wang X, Zhang H, Zhou Y, Chen L, Li Y, Wu L: **Increased EEG coherence in long-distance and short-distance connectivity in children with autism spectrum disorders**. *Brain Behav* 2020, **10**:e01796.

67. Di Lorenzo F, Ponzo V, Motta C, Bonnì S, Picazio S, Caltagirone C, Bozzali M, Martorana A, Koch G: **Impaired spike timing dependent cortico-cortical plasticity in Alzheimer's disease patients**. *J Alzheimer's Dis* 2018, **66**:983-991.

68. Avenanti A, Coccia M, Ladavas E, Provinciali L, Ceravolo MG: **Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke: a randomized trial**. *Neurology* 2012, **78**:256-264.

69. Pietrelli M, Zanon M, Làdavas E, Grasso PA, Romei V, Bertini C: **Posterior brain lesions selectively alter alpha oscillatory activity and predict visual performance in hemianopic patients**. *Cortex* 2019, **121**:347-361.

70. Tarasi L, Magosso E, Ricci G, Ursino M, Romei V: **The directionality of fronto-posterior brain connectivity is associated with the degree of individual autistic traits**. *Brain Sci* 2021, **11**:1443.

71. Ursino M, Serra M, Tarasi L, Ricci G, Magosso E, Romei V: **Bottom-up vs. top-down connectivity imbalance in individuals with high-autistic traits: an electroencephalographic study**. *Front Syst Neurosci* 2022, **16**:932128.

72. Tarasi L, Martelli ME, Bortoletto M, di Pellegrino G, Romei V: **Neural signatures of predictive strategies track individuals along the autism-schizophrenia continuum**. *Schizophr Bull* 2023, **49**:1294-1304, https://doi.org/10.1093/schbul/sbad105

73. Ippolito G, Bertaccini R, Tarasi L, Di Gregorio F, Trajkovic J, Battaglia S, Romei V: **The role of alpha oscillations among the main neuropsychiatric disorders in the adult and developing human brain: evidence from the last 10 years of research**. *Biomedicines* 2022, **10**:3189.

74. O'Hare L, Tarasi L, Asher JM, Hibbard PB, Romei V: **Excitation-inhibition imbalance in migraine: from neurotransmitters to brain oscillations**. *Int J Mol Sci* 2023, **24**:10093.