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Investigating the effects of cortico-cortical paired associative stimulation in the human brain: A systematic review and meta-analysis

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ABSTRACT

Recent decades have witnessed a rapid development of novel neuromodulation techniques that allow direct manipulation of cortical pathways in the human brain. These techniques, known as cortico-cortical paired stimulation (ccPAS), apply magnetic stimulation over two cortical regions altering interregional connectivity. This review evaluates ccPAS's effectiveness to induce plastic changes in cortical pathways in the healthy brain. A systematic database search identified 41 studies investigating the effect of ccPAS on neurophysiological or behavioural measures, and a subsequent multilevel meta-analysis focused on the standardized mean differences to assess ccPAS's efficacy. Most studies report significant neurophysiological and behavioural changes from ccPAS interventions across several brain networks, consistently showing medium effect sizes. Moderator analyses revealed limited influence of experimental manipulations on effect sizes. The multivariate approach and lack of small-study bias suggest reliable effect estimates. ccPAS is a promising tool to manipulate neuroplasticity in cortical pathways, showing reliable effects on brain cortical networks. Important areas for further research on the influence of experimental procedures and the potential of ccPAS for clinical interventions are highlighted.

1. Introduction

The nervous system operates as a complex network of interconnected neurons on a microscale level, and of structurally and functionally connected cortical areas on a macroscale level. Within the field of neuroscience, there is an ongoing common effort to map out the complexity of these cortical networks, aiming to elucidate the role of their composing elements in human cognition and behaviour with ever-increasing granular precision. The study of cortical networks in humans has been propelled by an accelerating development of novel forms of non-invasive brain stimulation (NIBS) that, rather than focusing on a single brain area, allow investigations of cortical pathways. These techniques, often referred to as dual-coil transcranial magnetic stimulation techniques, involve the application of pairs of TMS pulses over two brain areas at very short intervals (Ferbert et al., 1992; Hallett et al., 2017; Koch, 2020). The impact that the second (test) pulse has on brain activity is modulated by the first (conditioning) pulse if the first brain area is influencing the second brain area. In this way, it is possible to establish how activity in one brain area affects activity in the other area (Buch et al., 2010; Mars et al., 2009; Neubert et al., 2010; O'Shea et al., 2007). Importantly, when the pairs of TMS pulses are delivered in a repeated and coherent manner, it is possible to selectively potentiate, or

Abbreviations: TMS, Transcranial magnetic stimulation; NIBS, Non invasive brain stimulation; PAS, Paired associative stimulation; ccPAS, Cortico-cortical paired associative stimulation; LTP, Long term potentiation; LTD, Long term depression; STDP, Spike timing dependent plasticity; IPI, Interpulse interval; MEP, Motor evoked potentials; EEG, Electroencephalography; FMRI, Functional magnetic resonance imaging; EMG, Electromyography; ppTMS, Paired pulse transcranial magnetic stimulation; spTMS, Single pulse transcranial magnetic stimulation; CSE, Corticospinal excitability; ICF, Intracortical facilitation; SICF, Short-interval intracortical facilitation; SICI, Short-interval intracortical inhibition; CBI, Cerebellar-brain inhibition; TEP, TMS evoked potentials.

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strengthen, physiological connectivity between the two brain regions in an anatomically specific manner (Buch et al., 2011; Johnen et al., 2015; Sel et al., 2021; Trajkovic et al., 2023). Such a procedure is referred to as cortico-cortical paired associative stimulation (ccPAS). Unlike traditional TMS approaches targeting single brain regions with the aim to determine their causal involvement in specific cognitive domains (Silvanto and Cattaneo, 2017), ccPAS techniques enable unprecedented opportunities for understanding the causal influence that a cortical brain region exerts over another anatomically connected region through short- and long-range cortical connections.

ccPAS stems from the classical paired associative stimulation (PAS) protocol, which typically involves coupling peripheral stimulation with a TMS pulse delivered with precise timing over the cortex (Guidali et al., 2020; Stefan et al., 2000; Suppa et al., 2017). Specifically, peripheral-cortical PAS studies involve the repeated pairing of electrical stimulation of the median nerve immediately followed by a pulse of TMS over the primary motor cortex (M1) (Classen et al., 2004; Stefan et al., 2000). This protocol aims to modulate cortical excitability based on principles of Hebbian plasticity, where the timing of the stimuli is crucial. When the peripheral input arrives at the cortex just before the TMS pulse, it leads to long-term potentiation (LTP)-like effects; conversely, when the TMS pulse is delivered too early relative to the peripheral input, long-term depression (LTD)-like effects can be observed – demonstrating the importance of precise temporal coordination for synaptic strengthening or weakening (Classen et al., 2004; Stefan et al., 2000; Suppa et al., 2017; Wolters et al., 2003).

ccPAS differs from PAS in that it involves delivering two TMS pulses over two anatomically connected cortical sites. Specifically, ccPAS allows to selectively target and manipulate connectivity strength between two cortical regions (Hernandez-Pavon et al., 2023a, 2023b; Rizzo et al., 2009; Tarasi et al., 2024). The underlying physiological principles behind ccPAS (and PAS) are thought to tap into mechanisms of spike-timing dependent plasticity (STDP) and its evoked effects have been described as Hebbian in nature (Hebb, 1949; Koch, 2020). According to the principles of Hebbian-like STDP, the activation of presynaptic neurons immediately before postsynaptic neurons in a coherent and repeated manner leads to LTP (Caporale and Dan, 2008; Hebb, 1949; Jackson et al., 2006; Markram et al., 2011). By contrast, the firing of postsynaptic cells before the presynaptic cells usually induces LTD. These processes are crucial for refining neural circuits and balancing synaptic strengths within the brain.

The ccPAS protocol mimics this pre- and post-synaptic neuronal activation by repeatedly stimulating two cortical areas with two TMS coils following a precise temporal order and with a specific interpulse interval (IPI) both tailored to the anatomical and temporal properties of the cortical route (Borgomaneri et al., 2023; Buch et al., 2011; Hernandez-Pavon et al., 2023a, 2023b). Both precise temporal order of the two TMS pulses and precise IPI critically determine the impact of ccPAS in the targeted pathway. For example, in a given cortical network involving two regions where region A anatomically precedes and functionally influences region B, the repeated activation of A immediately before B results in an increase of the influence of A over B following the principles of LTP. By contrast, when the repeated stimulation is applied to the same cortical areas A and B but in the reversed temporal order – first pulse on B and second pulse on A – this is likely to result in a weakening of the influence of A over B (Buch et al., 2011; Koch, 2020; Sel et al., 2021; Turrini et al., 2024) through LTD mechanisms (Di Lazzaro et al., 2009; Markram et al., 2011). Yet, it is worth nothing that there are some conflicting and mixed findings regarding the ability of ccPAS to induce LTD (Buch et al., 2011; Turrini et al., 2024; for LTD; Chiappini et al., 2024b; Fiori et al., 2018; for LTP). However, in keeping with STDP rules, repeated simultaneous activation of both regions A and B (IPI=0ms), or the use of an IPI that does not follow the specific temporal pattern of the pathway, has little impact on cortical connectivity (e.g., (Borgomaneri et al., 2023; Koganemaru et al., 2009; Rizzo et al., 2009).

Under the assumption that the ccPAS protocol relies on STDP-like mechanisms, selecting the relevant IPI becomes critically important. Following the principles of information-based approaches to brain stimulation (Romei et al., 2016b), different methods have been developed to determine the temporal dynamics of specific cortico-cortical networks, thereby establishing optimal IPIs for administering ccPAS protocols on those networks. For instance, in networks involving the primary motor cortex (M1) it is possible to directly examine the influence of a functionally connected region, like the ventral premotor cortex (PMv), on M1 activity by using dual-coil TMS protocols (Hallett et al., 2017; Lafleur et al., 2016). By delivering a conditioning TMS pulse over PMv followed by a test pulse on M1 it is possible to establish the moment-to-moment functional influence of the conditioning pulse on M1 cortical excitability as measured by amplitude changes of the motor-evoked potentials (MEPs). Even though the impact of the first pulse in PMv is spatially circumscribed (Romero et al., 2019), the conditioning effect of PMv over M1 is thought to rely on the spread of activation to the M1 through the copious projections connecting the two regions (Cerri et al., 2003; Prabhu et al., 2009; Shimazu et al., 2004). Importantly, the temporal profile of the influence of PMv on M1 can be precisely mapped by systematically varying the IPI between the conditioning pulse and the test M1 pulse (Chiappini et al., 2024a; Davare et al., 2008; Fiori et al., 2017; Hallett et al., 2017; Reis et al., 2009). This approach is proven useful to delineate the temporal dynamics of cortico-cortical interactions within the motor system and is key to define the precise timing followed in ccPAS studies targeting M1 (Buch et al., 2011; Chiappini et al., 2020; Rizzo et al., 2009; Sel et al., 2021; Turrini et al., 2023c).

Moreover, studies investigating the visual cortex demonstrate that, just like it is possible to establish how activity in one motor area influences activity in M1, interactions between secondary and primary visual areas can also be examined with dual-coil TMS protocols. For example, pairing a pulse over the extrastriate motion area V5/MT+—which can evoke the perception of a moving phosphene— with a subsequent pulse over early visual cortex (V1/V2) can modulate phosphene perception within a specific temporal window (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005b, 2005a), which shows temporally specific V5/MT+-to-V1/V2 interactions. A number of ccPAS studies have capitalized on this approach to tailor their protocols (Chiappini et al., 2018; Di Luzio et al., 2022; Romei et al., 2016a).

More recently, other information-based approaches (Romei et al., 2016b) have been used to define the IPI, with successful outcomes. One study defined the IPI on the basis the communication though coherence framework; targeting the pathway connecting the left and right V5 areas - which resonates in the gamma band (40 Hz), the IPI was set to match the lag between peaks of the gamma oscillatory rhythm (Chiappini et al., 2022). A second study has combined TMS with electroencephalography (EEG) to characterise the temporal profile of connectivity between two cortical regions (Borgomaneri et al., 2023). Specifically, a single pulse of TMS was delivered over the posterior superior temporal sulcus (pSTS) while recording the EEG responses related to TMS activation of the pSTS with high-temporal resolution. By examining the EEG responses recorded from occipital sensors and estimating the signal originating from V1 using source reconstruction techniques, it was possible to pinpoint the timing at which V1 activity changed as influenced by the TMS pulse delivered over the pSTS and delineate the temporal connectivity profile between the pSTS and V1 (Borgomaneri et al., 2023). Thereafter, the ccPAS was tailored to follow this connectivity profile and evoked effects resulted in remarkable changes in electrophysiological and behavioural responses (Borgomaneri et al., 2023). This multimodal approach combining TMS with EEG responses lends itself to examine the temporal profile of the neural pathways involving areas where cortical activity cannot be measured with TMS alone. It should be noted that most ccPAS studies, regardless of the criteria used to define their critical IPI, have likely targeted polysynaptic pathways. For example, while M1 is only one synapse away from the PMv, both direct stimulation of these areas

and the activation spread between them are likely to involve the recruitment of interneurons (Buch et al., 2011; Davare et al., 2009). Although STDP mechanisms have been first demonstrated and reproduced in monosynaptic connections (e.g. Markram et al., 1997), it is plausible that the recruitment of polysynaptic pathways could yield similar plastic effects, provided that the pre- and post-synaptic timings are consistent with the temporal rules of STDP (Bi and Poo, 2001).

Overall, several studies demonstrated that ccPAS provides an overarching method to characterise neural dynamics in cortico-cortical brain networks and their causal role in cognition and behaviour. In addition, ccPAS offers the possibility to explore ways to induce transient changes in the human brain. Importantly, estimating its efficacy and the inter-individual variability of its effects is essential to determine the translational potential of ccPAS. It is therefore crucial to identify the factors that can lead to cross-study variance in neurophysiological and behavioural measures. To date, four review articles have summarized the effects of ccPAS on cortical networks including the motor (Guidali et al., 2021a), visual (Tarasi et al., 2024) and frontoparietal brain networks (Guidali et al., 2021b; Hernandez-Pavon et al., 2023a, 2023b). However, a systematic and quantitative assessment of the consistency and efficacy of the ccPAS effects on cortical dynamics and neuroplasticity is still missing. The present systematic review and meta-analysis aims to achieve two goals: first, to offer a comprehensive summary of the current evidence concerning the ability of ccPAS to manipulate multiple cortical networks in the healthy human brain; second, to quantitatively evaluate ccPAS efficacy to alter connectivity in a subset of studies targeting the motor and visual systems, with a focus on the moderators that mediate its efficacy. The meta-analysis focused on the motor and visual networks because they were the only suitable clusters that allowed a reliable assessment of the magnitude of the ccPAS effects. It is worth noting that the high heterogeneity of the ccPAS studies involving prefrontal pathways, along with the diversity of the measures used, prevent a meta-analytic evaluation of such ccPAS studies.

2. Materials and methods

2.1. Study selection and criteria

The systematic literature search was conducted following the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The PRISMA checklists and extracted data can be found at (https://osf.io/zyr6e/?view_only=79bb13da82474324bc1975f43adfe0ba). To qualify for this review, studies needed to include experiments that aimed to manipulate cortico-cortical pathways between brain regions using ccPAS as a technique. Also, studies needed to investigate functional and structural brain connectivity, neurophysiological responses, or behavioural outcomes. Finally, studies needed to be peer reviewed and based on human participants only. Considering this, all studies that had these characteristics were included in the analysis regardless of the age and gender of the participants reported.

This literature search identified a number of 975 studies which, after removal of duplicates, were subsequently screened and filtered (Fig. 1, Table S1).

2.2. Screening and selection process

Data extraction was concluded on April 2nd 2024. P.D.L., L.B. and S. T. oversaw the data collection process, and checked and resolved all inconsistencies between coders. The studies that were included in this systematic review exclusively employed the ccPAS protocol, defined as a repetitive stimulation of two distinct cortical regions using pairs of TMS with a predetermined and fixed IPI. Crucially, we considered protocols meeting the STDP criteria and adopted a causal approach of stimulation to modulate the connectivity between the targeted cortical sites. Based on this, no studies applying unspecific dual-coil TMS on distinct brain regions or ppTMS administered to the same brain area were included in our analysis.

Research papers involving healthy volunteers were considered for the systematic review, as the main aim was to synthetize the effects in such specific cohort. In line with this, studies involving clinical

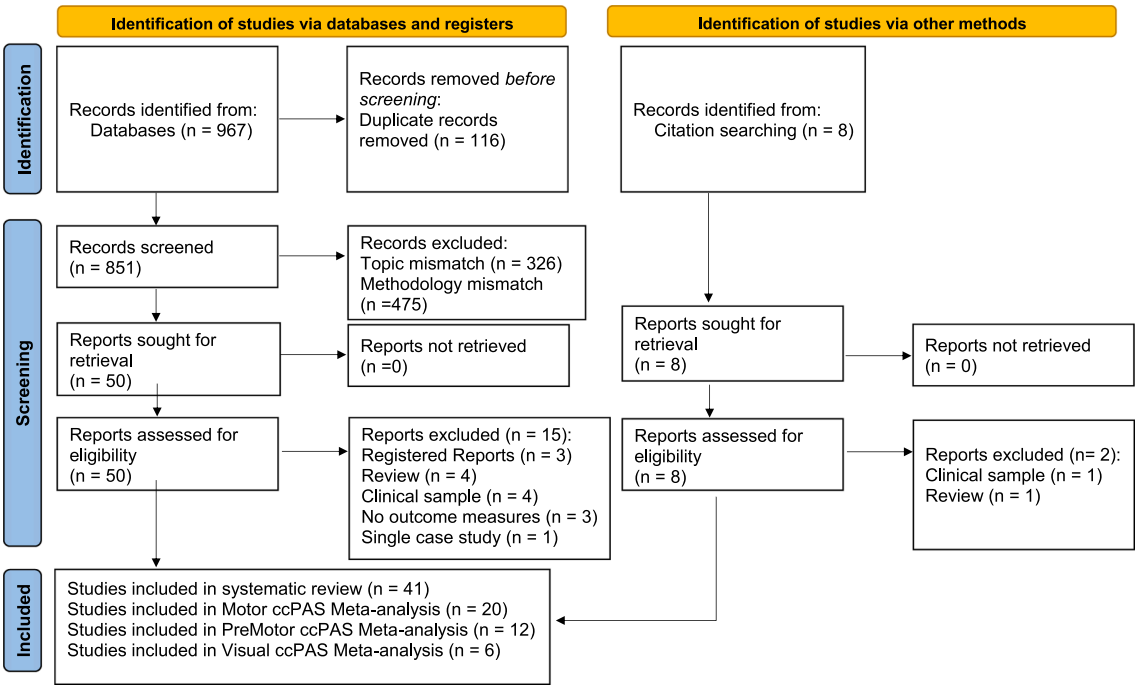

Fig. 1. PRISMA 2020 flow diagram. Literature search and selection procedures adopted for the systematic review and meta-analysis on ccPAS. This Includes searches of databases, registers and other sources. Adapted from (Page et al., 2021). For more information, visit: https://prisma-statement.org/.

populations were excluded (n=5), but they are briefly reported in the discussion section. No animal model studies were included. Single case reports (n=1, Goldenkoff et al., 2020), reviews, registered study protocols and theoretical perspectives were not considered in the results. The research findings comprised behavioural observations, electromyography (EMG), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI) results on healthy population. The objectives of this study were twofold: i) to summarize available evidence on the efficacy of ccPAS and ii) to provide a quantitative assessment of the effectiveness of the technique when applied to the motor and visual systems.

Included in the meta-analysis were studies assessing the effects during stimulation as well as those examining pre/post effects. Studies were first clustered based on the targeted cortical network. It was deemed appropriate to conduct meta-analyses only on clusters with at least 6 studies (Valentine et al., 2010). Therefore, it was not possible to synthetize findings about ccPAS application in other cortical networks owing to the paucity of studies and the variability of adopted protocols, cortical targets and outcome measures. Three main meta-analyses were performed. The first meta-analysis included all experiments that apply ccPAS on the motor control network ('Motor-ccPAS'), particularly studies that target M1 and measure changes in cortico-spinal excitability (CSE), which is taken as an index of the level of motor-related activity in M1. These criteria were chosen to reduce variability of the effects and to quantify the efficacy of ccPAS on CSE. In particular, the five pathways targeted involved the following brain areas: (1) posterior partietal cortex (PPC) and M1; (2) M1 and M1; (3) PMv and M1; (4) Cerebellar cortex (CCB) and M1; (5) Supplementary Motor Area (SMA) and M1. The second meta-analysis was performed on a cluster of studies targeting specifically the PMv-to-M1 pathway and that measure changes in CSE related to different TMS protocols such as single and paired-pulse TMS approaches ('Premotor-ccPAS'). Finally, the third meta-analysis focused on studies that use ccPAS to investigate the cortical dynamics of the visual network and to examine their role in visual perception ('Visual-ccPAS').

2.3. Effect size preparation

Effect sizes were either extracted directly from the selected publications or calculated based on the mean, standard deviation, and sample size values for the relevant outcome measures. If these measures were not explicitly reported, they were directly derived from the relevant plots and figures using the R package Juicr (Lajeunesse, 2021). When standard errors were reported, rather than standard deviations, these were back-transformed to standard deviations using a standardised formula based on the sample size (Higgins et al., 2019). Standardized mean difference corrected for small sample bias were computed as Hedges'g (Lakens, 2013), accounting for dependency of groups and assuming a within measurements correlation level of r = 0.7 (Fernández-Castilla et al., 2021; Scammacca et al., 2014). For consistency, all effect sizes were computed from data extracted from studies that involved a repeated measures design. This meant that effect sizes were computed from measurements recorded before and after the ccPAS protocol on the same participant sample.

Additionally, the absolute value of the standardized mean was used in order remove the polarity of the effects and consider only the net effect of ccPAS intervention: consequently, positive effect sizes quantify the magnitude of the observed effect relative to baseline. Multiple effect sizes were extracted from the studies included in each meta-analysis to account for the outcome measures recorded at different times (e.g., immediately before and after ccPAS, 30 minutes after ccPAS, etc.) or testing different variables (e.g., spTMS, ppTMS).

2.4. Data analysis

Most of the studies included in the meta-analyses reported more than two effect sizes; in these instances, effect sizes are likely to relate to one another (Wibbelink et al., 2017). To prevent interdependence of effect sizes, we used 3-level random effects models often used when examining effect sizes from correlated or nested data (Cheung, 2019). The 3-level meta-analysis enabled us to account for the hierarchical nature of the data (e.g., effects sizes nested within studies) and to preserve useful information without undermining statistical power (Assink and Wibbelink, 2016; Van Dam et al., 2018).

Models were fitted with a restricted maximum likelihood (REML) estimation method, as such algorithm tends to provide approximately unbiased estimates of the amount of heterogeneity (Langan et al., 2019; Veroniki et al., 2016; Viechtbauer, 2005). t- and F-distributions were used for making inferences applying an improved method for approximating the degrees of freedom (Viechtbauer and Cheung, 2010). Prediction intervals were computed for every estimated effect. A 95 % prediction interval shows a range of values where future studies on similar topics are likely to find the true effect. (Higgins et al., 2009; IntHout et al., 2016). In our specific case, an interval including only positive values represents with 95 % of probability that other studies in that domain will find a significant ccPAS effect. For each cluster of studies, a main meta-analysis was conducted across every effect regardless of any potential moderator, this was done to establish the efficacy of the ccPAS protocol and the size of the overall effect. Hedge's g values of 0.2, 0.5 and 0.8 are conventionally considered small, medium and large, respectively (Cohen, 1992, 1988).

2.4.1. Statistical heterogeneity

With the application of 3-level models we were able to decompose heterogeneity in sampling variance of the observed effect sizes (level 1), variance within studies (level 2) and variance between studies (level 3; (Cheung, 2014; Konstantopoulos, 2011). We calculated two indices to assess statistical heterogeneity. The first index (I^2) captures the proportion of total variance in effect estimates related to heterogeneity, as opposed to the sampling error (25 %, 50 %, and 70 % representing low, moderate, and substantial heterogeneity, respectively; Higgins et al., 2003). The second index represents the degree of variance according to differences or similarities within studies (τ^2 within) and between studies (τ^2 between), where a zero value indicates no heterogeneity. When the heterogeneity is moderate the model can include moderators to examine the impact of these moderators on level 2 and level 3 variance, and also the overall effect.

All statistical analyses were performed using the package metafor (Viechtbauer, 2010), the package dmetar in R (Harrer et al., 2021), and the package metaviz (Kossmeier et al., 2020a) in the R statistical platform (R Development Core Team, 2019).

2.4.2. Moderator/Subgroup analysis

Additional multilevel meta-analyses were conducted to include additional influential factors (i.e., moderators) whenever necessary. This was done to examine whether the effectiveness of the protocol depended on the characteristics of the studies, and also to account (at least in part) for high heterogeneity in the estimated effects. Moderators were chosen across the meta-analyses based on relevant research questions and their frequency across the studies.

In the main 'Motor-ccPAS' meta-analysis, we included the stimulated network (M1-M1, PMv-M1, CB-M1, PPC-M1, SMA).

In the 'Premotor-ccPAS' meta-analysis, focusing on the PMv-M1 pathway, we considered the influence of four different moderators: *Cognitive state*, *Tested Cortical Circuit*, *Timing* and *Stimulation Intensity*.

In the 'Visual ccPAS' meta-analysis, only the moderator of '*Timing*' was included.

3-level mixed-effect effects models were used to examine if these moderators influenced the effects of ccPAS compared to overall effect meta-analyses data.

2.4.3. Publication Bias and sensitivity analysis

Publication bias was investigated by means of visual inspection of the raw effect sizes distribution using funnel plots contrasting individual effects and their precision (inverse standard error, (Lau et al., 2006)). Contour-enhanced and power-enhanced funnel plots were adopted to include information of statistical significance and power relative to the expected true value of the effect (Kossmeier et al., 2020b; Peters et al., 2008). Multilevel extensions of Egger's regression method were used to statistically test presence of bias (Egger et al., 1997; Fernández-Castilla et al., 2021) using a modified standard error formula proposed to deal with correlation (Pustejovsky and Rodgers, 2019). PET-PEESE conditional procedure was used to check limit estimates using the standard error (PET) and the sampling variance (PEESE) as predictors (Stanley and Doucouliagos, 2014) to obtain bias-corrected estimates of the effects. P-curve methods were also used to investigate the likelihood of publication bias occurring due to significance levels and p-hacking (Simonsohn et al., 2014). Additional sensitivity analyses were performed to assess the robustness of the findings. To this aim, we merged outcomes considering groups from a single study to control for unit of analysis errors, and run univariate models with aggregated data (see supplementary analysis).

3. Results

We identified 41 studies that employed the ccPAS technique. A summary of the studies, including information about the stimulated networks and the tested measures is provided in Fig. 2. The systematic review of the studies is organised by targeted brain regions.

3.1. Inducing and measuring cortico-cortical plasticity in motor control brain areas

3.1.1. Investigating connectivity in the primary motor cortex with ccPAS protocols

The ccPAS protocol was first developed by Rizzo and colleagues to examine interhemispheric M1 connections (Rizzo et al., 2009). Connectivity between the two M1 cortices is crucial to movement control and execution; specifically, each M1 exerts a powerful inhibitory influence over the contralateral homologue through transcallosal connections. The M1-M1 pathway has been extensively investigated in humans with dual-coil TMS techniques which demonstrated that the stimulation of one M1 shortly (6–8 ms) before the other inhibits the excitability of the second stimulated site, a phenomenon called interhemispheric inhibition (IHI), an index of effective connectivity between the two M1 regions (Ferbert et al., 1992; Perez and Cohen, 2009).

Capitalising on previous dual-coil TMS studies targeting the M1-M1 pathway, Rizzo and colleagues demonstrated that the repeated stimulation of the two areas through ccPAS can modify the influence that the contralateral M1 exerts over ipsilateral M1 (Rizzo et al., 2011, 2009). In particular, Rizzo and colleagues found that administering a ccPAS protocol with IPIs commonly used to investigate M1-M1 interhemispheric interactions (i.e., 8, 9 or 10 ms IPI; Ferbert et al., 1992) results in a decrease of the inhibitory influence of the contralateral M1 over the ipsilateral M1 (i.e. reduced IHI), and an increase in CSE of the ipsilateral

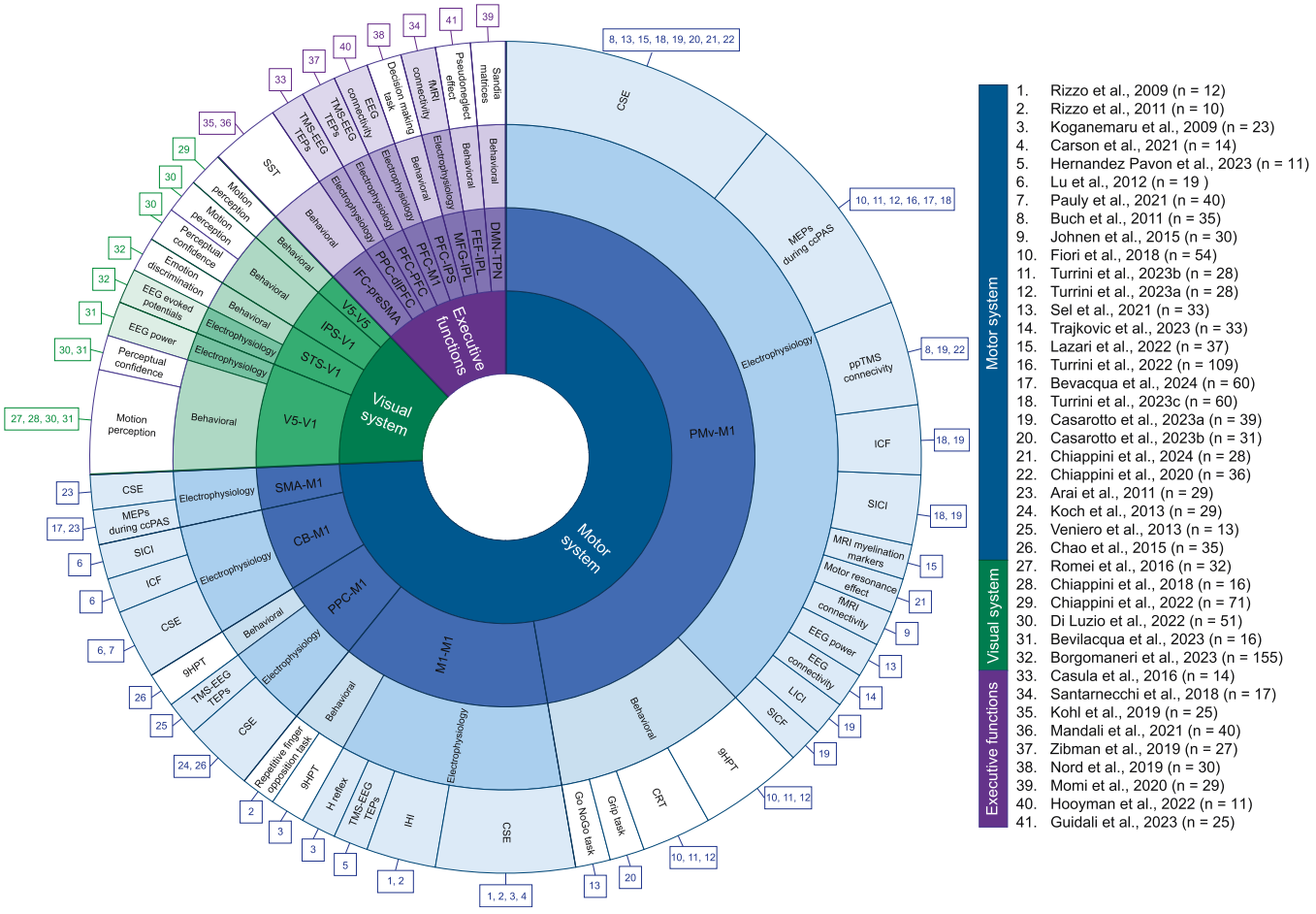

Fig. 2. Systematic review results. Hierarchical chart of ccPAS studies in healthy humans included in the systematic review. Studies are sorted radially depending on the domain (Visual, Motor and Executive), the network (e.g., PMv-M1), the investigation (e.g., behavioural) and the measure tested (e.g., MEPs). Sample size is reported for each study.

M1 (Rizzo et al., 2009). These effects were observed 30 minutes after the ccPAS intervention and remained present up to 60 minutes post-intervention. No changes were observed when the ccPAS was delivered with an IPI that did not follow the temporal profile of the pathway (1 ms IPI, or multiple IPIs in random order). A follow-up study from the same group showed that potentiating the M1-M1 route with ccPAS also improved manual performance, as indexed by faster response times in repetitive finger opposition movements up to 30 minutes after the ccPAS intervention (Rizzo et al., 2011).

In the same line, Koganemaru and colleagues (Koganemaru et al., 2009) also found a decrease of IHI and increase of CSE resulting from strengthening M1-M1 connections with a ccPAS protocol adopting a 15 ms IPI, which is also in keeping with the IPI used to investigate M1-M1 interactions (e.g., Ferbert et al., 1992; Perez and Cohen, 2009). Neurophysiological changes were observed together with improved performance in the 9-Hole Peg Test, a widely used task that measures manual dexterity, finger coordination, and fine motor skills by assessing the time taken to insert and remove nine pegs from a pegboard (Mathiowetz et al., 1985). By also measuring the magnitude of the H-reflex, Koganemaru and colleagues demonstrated that ccPAS-induced effects could not be ascribed to spinal mechanisms (Koganemaru et al., 2009). Moreover, Carson and colleagues showed further support that strengthening the connections from the right M1 to the left M1 with ccPAS (6 ms IPI) leads to a decrease of IHI lasting around 20–30 minutes (Carson et al., 2021).

More recently, Hernandez-Pavon and colleagues (Hernandez-Pavon et al., 2023a, 2023b) combined TMS with EEG recordings to study the changes in effective connectivity induced by M1-M1 ccPAS. They found that potentiating the connections from the left M1 to the right M1 results in an enhanced connectivity in the left-to-right M1-M1 pathway as indexed by an increased amplitude of the early components (i.e., 5–20ms) of TMS evoked potentials (TEPs) recorded in the right M1. This effect was long-lasting (up to 60 minutes), and it was only present when the IPI accorded with the temporal dynamics of the left-to-right M1-M1 cortical route (14 ms) following the principles of STDP – i.e., a shorter IPI (4 ms) induced LTD mechanisms decreasing TEPs amplitude.

In summary, these studies collectively suggest that targeting the pathway connecting the right and the left M1 with ccPAS leads to a decrease in IHI, along with enhanced CSE and improved manual performance. It is worth noting that the functional role of the contralateral M1 is to inhibit the cortical activity of the ipsilateral M1. Therefore, in line with the principles of Hebbian-like LTP, strengthening the M1-M1 pathway should increase the inhibitory influence of the contralateral M1 site over the ipsilateral M1. However, the current evidence shows the opposite results, suggesting that repeated inhibitory signalling reduces the efficacy of interhemispheric inhibitory connections and enhances excitatory mechanisms. Similar paradoxical effects have been observed at inhibitory GABAergic synapses, where coincident pre- and postsynaptic activity can shift the reversal potential of GABAergic activity, thereby decreasing inhibition and increasing net excitability (Woodin et al., 2003). This may explain the findings following M1-M1 ccPAS, highlighting how synaptic plasticity dynamically regulates cortical excitability.

It is important to note that previous investigations involved right-handed individuals. Arguably, the synaptic efficacy in the left-to-right M1-M1 pathway (responsible for inhibiting the left hand) may be greater in the left-to-right M1-M1 pathway as opposed to the pathway connecting the right with the left M1. This functional asymmetry in right-handed individuals may therefore lead to distinctive functional changes after the ccPAS intervention depending on the direction of the stimulation – i.e., left-to-right M1 ccPAS as opposed to right-to-left M1 ccPAS. Despite previous attempts to systematically investigate this functional asymmetry (Rizzo et al., 2011, 2009), the small sample size used in previous studies combined with the large interindividual variability in MEP responses (a well-established occurrence in the brain stimulation field; Sommer et al., 2002) might explain the disparity between the observed and the expected pattern of results. A well-powered investigation that systematically contrasts the effects of left-to-right *versus* right-to-left M1 ccPAS should address this issue.

3.1.2. The study of the route connecting the cerebellum and the primary motor cortex

Lu and collaborators (Lu et al., 2012) investigated whether increasing long-range connectivity between the cerebellum and the M1 with ccPAS would result in M1 cortical excitability changes. The cerebellum has a particularly important role in posture control and movement, and in motor learning. There are dense connections between the cerebellum and the motor cortex, especially projecting from the lateral part of the cerebellum and exerting a strong inhibitory effect over M1 cortical excitability (cerebellar-brain inhibition, CBI) (Ugawa et al., 1995). Thus, potentiating inhibitory connections between the lateral cerebellum and M1 is likely to result in decreased M1 cortical excitability. Lu and colleagues (Lu et al., 2012) tested this hypothesis by repeatedly stimulating the right lateral cerebellum before the left M1 with ccPAS using different IPIs: 2 ms, 6 ms, 10 ms, or a combination of 2 ms and 10 ms. Consistent with the hypothesis, the results showed a decreased CSE after ccPAS delivered with IPIs that followed the timing of information communication for this pathway (6 ms, 10 ms); these CSE changes lasted about 60 minutes. By contrast, ccPAS with a short IPI of 2 ms increased CSE in line with the principles of Hebbian-like LTD. After every ccPAS protocols, irrespective of the adopted IPI, a reduction in the local M1 intracortical inhibition (i.e., SICI) and in CBI was observed. This means that the overall decrease in excitability in the cerebellum and M1 cannot be attributed to any specific manipulation of the cerebellar-M1 route, but rather to the more repeated activation of these two brain elements. A recent study replicated these findings observing that cerebellar-to-M1 ccPAS with a 6 ms IPI induced an immediate decrease in M1 CSE (Pauly et al., 2021). Overall, these results show that it is possible to modulate the functional influence of the cerebellum on the motor system, providing further support for the efficacy of ccPAS to investigate long-range connections.

3.1.3. Examining the cortico-cortical connections between the ventral premotor cortex and the primary motor cortex

Most of the ccPAS studies in the motor control system focus on the pathway connecting the ventral PMv and M1. It is well-established that the PMv-M1 pathway, embedded in the wider dorsolateral sensorimotor stream, is a key cortical motor circuit primarily involved in fine motor control (Fogassi et al., 2001; Lemon, 2012; Rizzolatti et al., 2014). This pathway has been studied in humans by means of dual-coil TMS. Studies have shown that by stimulating PMv shortly before stimulation of M1, it is possible to influence M1 activity. These studies have suggested the existence of both short-latency (peaking at 6/8ms IPI) (Buch et al., 2010; Davare et al., 2011, 2009, 2008; Neubert et al., 2010) and long-latency (IPI $>$ 40 ms), likely indirect, connections between PMv and M1 (Fiori et al., 2016). Given the extensive literature describing the structural and functional properties of the PMv-M1 circuit (Buch et al., 2010; Cerri et al., 2003; Davare et al., 2009; Prabhu et al., 2009; Shimazu et al., 2004), this pathway serves as a valuable testbed to examine the effects of manipulating connectivity strength with ccPAS.

Converging evidence suggests that strengthening the physiological direct connections between PMv and M1 with ccPAS leads to a greater functional influence of PMv on M1 resulting in M1 activity changes (Buch et al., 2011; Fiori et al., 2018; Johnen et al., 2015; Sel et al., 2021; Turrini et al., 2023c). These effects have been recorded as changes in M1 CSE, intracortical inhibition and facilitation metrics, effective connectivity as measured with dual-coil TMS, functional connectivity assessed with fMRI and EEG, as well as behavioral performance.

The first study targeting the PMv-M1 pathway by Buch and colleagues (2011) showed that repeated stimulation of PMv and M1 with ccPAS administered at rest (8 ms IPI) increases M1 CSE tested during movement production (Buch et al., 2011; see also Sel et al., 2021), i.e.,

when PMv normally exerts an excitatory influence over M1 (Davare et al., 2009). In contrast, there was no change in CSE when tested at rest (Buch et al., 2011). Moreover, this study found that the same ccPAS protocol also enhanced the inhibitory influence of PMv over CSE excitability in settings in which PMv inhibits M1, i.e., during rest (Buch et al., 2011), suggesting increased PMv-M1 connectivity. Such effects were anatomically specific, i.e. the application of ccPAS over a parallel premotor-motor network comprising the pre-SMA and M1 did not affect the influence of PMv over M1 (Buch et al., 2011). Changes in PMv-M1 connectivity strength developed quickly, persisted for at least an hour, and began to fade 3 hours post-intervention (Buch et al., 2011).

Effects of PM-M1 ccPAS on cortico-cortical connectivity have also been observed when using longer pre-and postsynaptic intervals by Chiappini and colleagues (Chiappini et al., 2020). Informed by long-latency PMv-M1 interactions assessed with dual-coil TMS (Fiori et al., 2017, 2016), this study assessed the effect of PM-M1 ccPAS delivered with an IPI of 40 ms, which taps into the long-range, indirect route connecting PMv and M1. The results showed an increased functional influence of PMv over M1 assessed using dual-coil TMS as previously reported (Buch et al., 2011). However, these connectivity changes did not last as long and were less anatomically specific than the PMv-M1 ccPAS at 8 ms IPI targeting direct, short-range connections (Chiappini et al., 2020). Also, this study did not report a change in M1 CSE at rest.

In contrast to these studies, others have reported changes in M1 CSE, both during and after the administration of the PMv-M1 ccPAS protocol. Turrini et al. (2022) showed in a large sample (>100 participants) that PMv-to-M1 ccPAS leads to a gradual increase of M1 CSE evolving throughout the ccPAS protocol. Similar findings were previously observed in a smaller cohort (Fiori et al., 2018) and later replicated by other studies (Bevacqua et al., 2024; Turrini et al., 2023c, 2023b). This discrepancy may be attributed to different ccPAS parameters used: while Buch et al. (2011) and Chiappini et al. (2020) employed parameters (IPI and stimulation intensity) targeting inhibitory PMv-M1 interactions, Turrini et al. (2022) designed a ccPAS protocol based on excitatory PMv-M1 interactions (e.g., (Chiappini et al., 2024a; Turrini et al., 2023c).

By contrast, reversing the pulse order – i.e., M1-to-PMv ccPAS - did not lead to consistent changes during ccPAS, as only a trend towards inhibition was observed in this study (Turrini et al., 2022). However, two recent studies reported reduced CSE during M1-to-PMv ccPAS (Bevacqua et al., 2024; Turrini et al., 2024).

Changes in PMv-M1 coupling induced by PMv-to-M1 ccPAS also impact the levels of intracortical inhibition within M1. Turrini and colleagues (Turrini et al., 2023c), investigated whether manipulating PMv-M1 connectivity influences M1's local interneuron circuits. The study found an increase in CSE and a decrease in short interval intracortical inhibition (SICI) measured at rest after the ccPAS intervention, suggesting that the protocol elicits a suppression of specific inhibitory GABAergic mechanisms within M1 (Turrini et al., 2023c). On the contrary, no differences in intracortical facilitation (ICF) were observed. Collectively, these results indicate that potentiating the influence of PMv on M1 increases M1 motor-related activity at rest.

These results are complemented and extended by findings by Casarotto and colleagues (Casarotto et al., 2023b, 2023a). The authors suggest that higher-order premotor regions, such as the PMv, contribute to the generation of the second indirect descending wave (I2-wave), which can be elicited by M1 stimulation (Cattaneo et al., 2005). I-waves are thought to be generated by the repetitive firing of cortical neurons in response to TMS and represent the summation of excitatory and inhibitory inputs in the corticospinal pathway (Rossini et al., 2015). Therefore, Casarotto et al. (2023) set out to investigate whether manipulating the functional influence of PMv on M1 with ccPAS would affect the I2-wave by measuring short-interval intracortical facilitation (SICF 2.5 ms) in M1, which is thought to tap into the mechanism supporting the I2-wave, before and after ccPAS (Casarotto et al., 2023a). Results showed that PMv-to-M1 ccPAS leads to an increase in CSE and a specific reduction of SICF 2.5 ms suggesting that strengthening the PMv-M1 pathway selectively impacts the I2-wave circuits.

In a subsequent study, Casarotto et al., (2023) aimed to target specific populations within M1 by adopting either an anterior-posterior (AP) or a posterior-anterior (PA) induced current of the M1 TMS coil (Casarotto et al., 2023b). The traditional PA current orientation is thought to target deeper neuronal populations, whereas inducing an AP current flow preferentially activates superficial populations. The standard ccPAS protocol (with the M1 coil inducing PA currents) increased CSE, replicating prior findings. Interestingly, rotating the M1 coil so to induce AP currents during ccPAS, allowed authors to stimulate superficial layers of M1 thought to be the main target of PMv projections relevant to precision grip. This ccPAS protocol selectively enhanced CSE during precision grip, but not power grip. Based on these effects, the authors concluded that more superficial M1 neuronal populations, influenced by the PMv input, are primarily engaged in executing precision grasping.

Importantly, it was observed that increasing connectivity between PMv and M1 with ccPAS can also improve performance on a task involving precision grasping (Fiori et al., 2018;Turrini et al., 2023a). For example, enhancing PMv-M1 connectivity by ccPAS (8 ms IPI) in a group of younger adults results in increased motor performance in the 9-Hole Peg Test – an established visuomotor task that requires participants to grasp, manipulate and insert small pins into a board (Mathiowetz et al., 1985; Oxford Grice et al., 2003). While following PM-to-M1 ccPAS participants showed reduced execution time at this task, reversing the order of the ccPAS pulses (M1-to-PMv ccPAS) did not lead to changes in motor performance on the same task. The effect was later replicated in young individuals but, interestingly, the application of PMv-to-M1 ccPAS did not lead to changes in motor performance in the 9-Hole Peg Test in a sample of elderly participants (Turrini et al., 2023a).

Beyond its role in voluntary motor control, the PMv also plays a crucial role in action observation and action understanding (Avenanti et al., 2013; Urgesi et al., 2014). Thus, the route connecting PMv with M1 is thought to support motor resonance and to regulate muscle specific M1 activation linked to observation of other's movements (Avenanti et al., 2007; Fadiga et al., 1995; Koch et al., 2010). In this line, recent evidence suggests that increasing PMv-to-M1 connectivity using ccPAS transiently enhances motor resonance effects in M1 during action observation (Chiappini et al., 2024b). This highlights the potential of ccPAS as a tool for investigating the plasticity of the social brain in both healthy and clinical populations (see also Turrini et al., 2024).

ccPAS protocols can be readily combined with neuroimaging methods providing an ideal opportunity to test hypothesis of human brain functioning. Common to many theories of brain functioning is the notion that the synchronisation of EEG oscillations is a key element in communication between brain areas (Fries, 2015, 2005; Salinas and Sejnowski, 2001). Importantly, it is thought that it is only possible for different sets of neurons to oscillate synchronously when they share a common physiological substrate (van Ede et al., 2018; Wang, 2010). Sel and colleagues (Sel et al., 2021; Trajkovic et al., 2023) tested this hypothesis in the PMv-M1 circuit carrying out two ccPAS interventions that have been established to either transiently increase –PMv-to-M1 ccPAS– or decrease –M1-to-M1 ccPAS– the strength of PMv projections to M1. The contrast between EEG activity measured in the alpha, beta, and theta frequency bands during a motor Go-No Go task before and after ccPAS revealed that increasing PMv-M1 physiological connectivity increases power in the beta and theta frequency bands when going and stopping, respectively. By contrast, delivering M1-to-PMv ccPAS reduces beta activity during Go trials and theta activity during No-Go trials (Sel et al., 2021). Moreover, manipulation of the interregional PMv-M1 coupling also changes EEG phase synchrony between activities in both areas during rest. This is, PMv-to-M1 ccPAS leads to increased phase synchrony in alpha and beta bands, while reversed order M1-to-PMv

ccPAS leads to decreased theta phase synchrony. These changes visible at rest, are also predictive of changes in oscillatory power in the same frequencies during movement execution and inhibition, respectively (Trajkovic et al., 2023). These findings highlight the ability of the ccPAS technique to investigate the link between the physiology of the motor network and the resonant frequencies mediating its interactions.

The effects of ccPAS over the functional and structural properties of the PMv-M1 pathway have also been established by combining ccPAS with magnetic resonance measures. Johnen and colleagues examined changes in the coupling of blood oxygen level dependent (BOLD) signals in PMv and M1 before and after ccPAS (Johnen et al., 2015). From this experiment, it is clear that the changes in PMv-M1 coupling resulting from the ccPAS intervention are prominent between the stimulated areas themselves, but they also extend to other motor association areas with which PMv and M1 are closely interconnected in frontal and parietal cortex (Johnen et al., 2015). Importantly, this study and a subsequent study by Lazari et al. (2022) also reported decreased connectivity between the stimulated brain areas and parallel non-stimulated pathways. This suggests that the influence of ccPAS primarily affects the stimulated pathway but can extend to a more systemic level.

Lazari et al., (2022) used magnetic resonance (MR)-based quantitative myelin markers to investigate changes in myelinated white matter tracts before and after the ccPAS intervention over PMv and the contralateral M1 (Lazari et al., 2022). The results showed that this interhemispheric PMv-to-M1 ccPAS leads to an increase in CSE, but also in myelination of the stimulated fibre bundle. Notably this was only the case when ccPAS was applied with an IPI consistent with pre- and postsynaptic activation of PMv and M1 (6 ms) following the principles of Hebbian-like long-term potentiation. This study demonstrates that Hebbian activity-dependent plasticity extends beyond synaptic changes and can be observed in human white-matter fibers.

3.1.4. Manipulating interregional connectivity in the pathway connecting the supplementary motor area and the primary motor cortex

Arai and colleagues (Arai et al., 2011) manipulated and measured physiological connectivity between the supplementary motor area (SMA) and M1 with ccPAS. The authors recorded MEPs before, during, and after ccPAS involving different IPIs. They found that stimulating the SMA 6 ms before M1 increased M1 CSE. By contrast, reversing the order of the TMS pulses, i.e., first pulse over M1 and second pulse on SMA, decreased M1 CSE but this was only true when the IPI between the M1 and SMA was 15 ms. Both LTP-like and LTD-like effects were still present 30 minutes after ccPAS. In contrast, a non-significant facilitation was observed when applying M1-to-SMA ccPAS with an IPI of 10 ms (Arai et al., 2011).

In a further study, Bevacqua et al., (2024) also showed a CSE enhancement during the administration of a SMA-to-M1 ccPAS protocol delivered with 8 ms IPI (Bevacqua et al., 2024). However, increased CSE activity was also observed in the reversed M1-to-SMA ccPAS condition with 8 ms IPI. The contrasting results may be explained by the difference in IPI adopted in the reversed M1-to-SMA ccPAS protocol in the two studies. While these studies report consistent CSE increase during SMA-to-M1 ccPAS with early IPIs of 6–8ms, they show distinct effect during M1-to-SMA depending on the ISI employed.

3.1.5. Investigating the circuit connecting the Posterior parietal cortex and the primary motor cortex with ccPAS

The systematic literature review identified 3 studies that have explored the use of ccPAS to manipulate connectivity between parietal and motor regions. It is well-established that the parieto-motor circuits support movement planning and execution, having an important role in integrating sensory feedback and spatial information to guide motor actions. In particular, the route connecting the posterior parietal cortex (PPC) and the M1 has an especially important role in movement adaptation to external changes (Andersen and Cui, 2009; Tanaka et al., 2009). The three studies targeted PPC in a site corresponding to the posterior part of the intraparietal cortex.

The first study using ccPAS to examine the PPC-M1 route showed that potentiating the functional influence of the PPC over M1 with IPIs of 5 or 20 ms led to decreased M1 CSE at rest. They also observed that reversing the order of stimulation, i.e., M1-to-PPC ccPAS using the same IPIs, increased CSE during rest. Such changes were observed up to 20 minutes after the stimulation (Koch et al., 2013). Interestingly, the effect depended on both current direction and ongoing brain state: if ccPAS is applied during muscular contraction, or if the M1 coil is oriented with an AP direction, the direction of effects was inverted – i.e. ccPAS-to-M1 ccPAS increased CSE, while M1-to-PPC ccPAS decreased CSE measured in M1 (Koch et al., 2013; Veniero et al., 2013). To further examine the functional dynamics of the PPC-M1 pathway, Veniero and colleagues (Veniero et al., 2013) combined ccPAS with TMS-EEG and measured the TMS-evoked potentials (TEPs) before and immediately after ccPAS. The comparison of the TEPs recorded prior and following PPC-to-M1 ccPAS (5 ms IPI) revealed increase amplitude in the TEPs recorded over M1 and decreased CSE; by contrast, the reversed M1-to-PPC ccPAS protocol led to decreased TEP amplitudes in M1. When measuring TEPs from the PPC no amplitude modulations were observed. Connectivity analysis revealed that increased TEP amplitude in the PPC-to-M1 ccPAS condition (5 ms IPI) – which is thought to potentiate PPC-M1 coupling, was accompanied by increased beta coherence between the two component areas. On the other hand, decreased TEP amplitudes resulting from weaking the PPC-M1 pathway with a M1-to-PPC ccPAS protocol co-occurred with an increase of alpha coherence between the two nodes of the targeted route (Veniero et al., 2013).

It is noteworthy that a later study conducted by Chao et al. employed a longer IPI of 8 ms and observed an increase in M1 CSE measured at rest that emerged only at 60 minutes after PPC-to-M1 ccPAS (Chao et al., 2015). The effects of PPC-to-M1 ccPAS were also tested on motor performance using the Purdue pegboard test, but no significant changes were observed as a result of increasing the influence of PPC on M1. These seemly contradictory results may be explained by the different experimental approach taken by Chao et al. (Chao et al., 2015). In this experiment, MEP recordings were taken immediately after the motor task. It is therefore possible that enhanced motor excitability resulting from performing the task could have influenced M1 activity measured directly after the task. This hypothesis would be in line with the results observed by Koch et al. (Koch et al., 2013) when ccPAS was administered during muscle contraction.

3.2. Meta-analysis of ccPAS studies of the motor system

3.2.1. Motor-ccPAS meta-analyses

The findings of all studies that targeted circuits connected to the primary motor area (M1) with ccPAS and tested its impact on CSE (n=21, k=65) were subsequently analysed through a meta-analysis. The studies included tested an overall sample of 414 participants.

The analysis showed that the pooled average outcome based on the 3-level model was g= 0.52 (95 % CI [0.42 0.62) and that such effect size differed significantly from zero (t(20)=10.68 p<0.0001). The observed outcomes ranged from g=0.038–1.40, and the 95 % prediction interval [0.09 0.95] for the true effect of the studies indicated the same direction as the estimated average outcome. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Fig. 3. The estimated variance components were $\tau^2_{\text{Level 3}}$=0.019 and $\tau^2_{\text{Level 2}}$=0.018. This means that $I^2_{\text{Level 3}}$= 22.44 % of the total variation was attributed to between-cluster, and $I^2_{\text{Level 2}}$= 20.23 % to within-cluster heterogeneity.

Visual inspection of publication bias using funnel plots suggested no apparent asymmetry in effect size distribution (Fig. 4). Result of multilevel Egger's test confirmed the absence of a significant relationship between effect size and sampling error (p= 0.72, Fig. S1). Adjusted

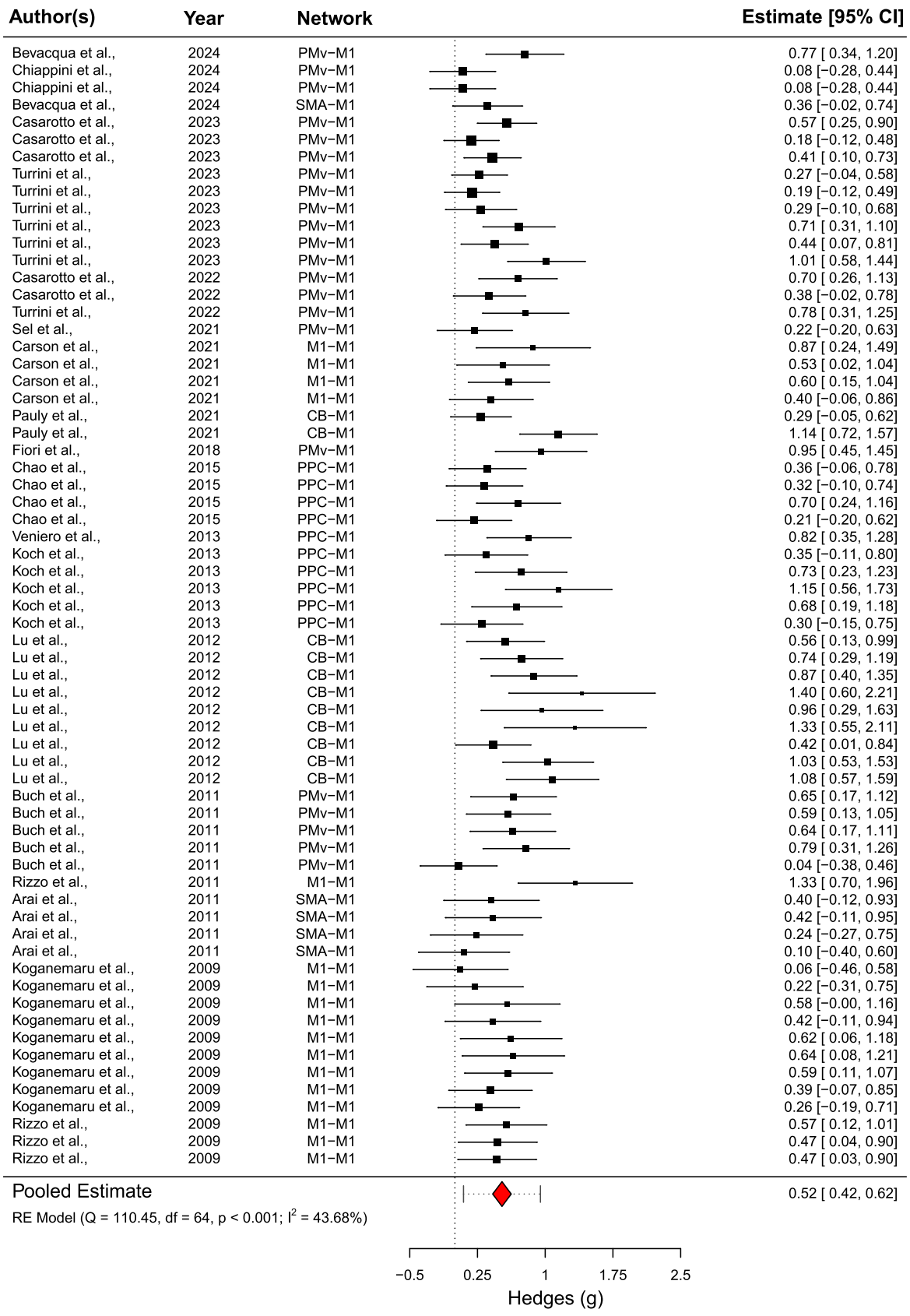

Fig. 3. Forest Motor ccPAS. Forest plot of absolute effect sizes (Hedges' g) for all studies included in the motor ccPAS meta-analysis. The pooled estimate and 95 % confidence interval (red diamond) is reported with 95 % prediction interval (dashed horizontal line) and compared to null effect (dashed vertical line). The size of each black square indicates the weight of the effect size in the combined analysis with 95 % CI (black lines). Multiple effect sizes are reported for the studies.

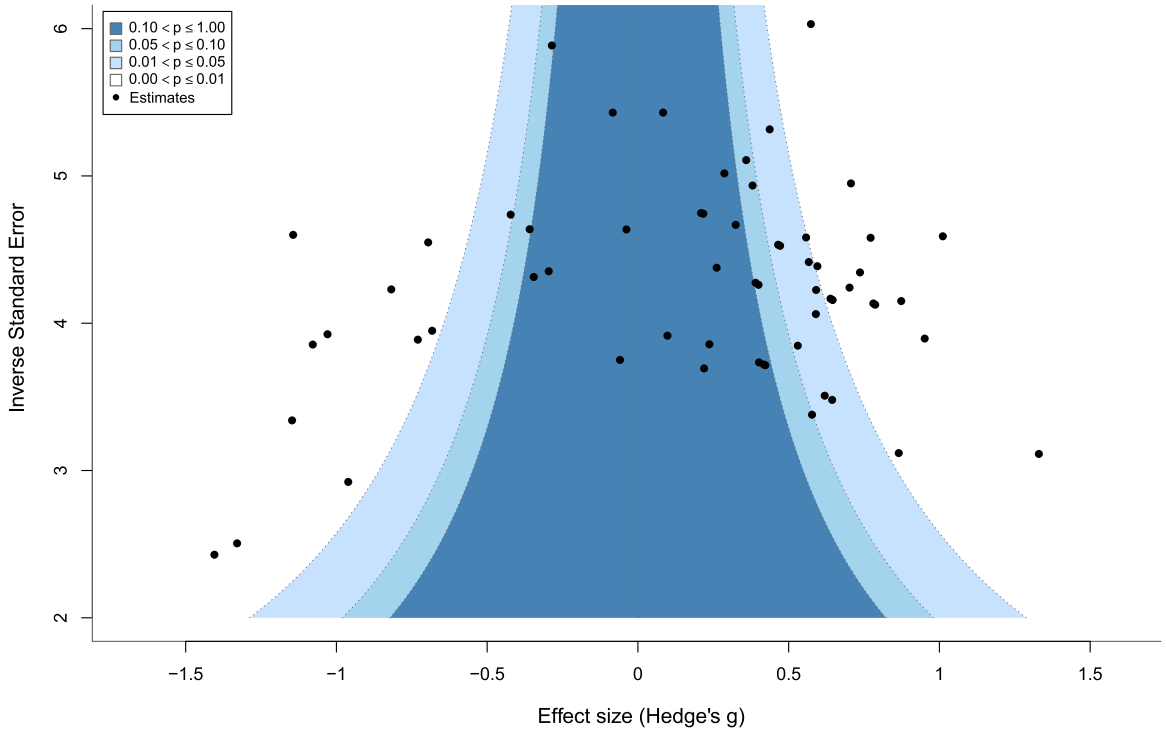

Fig. 4. Funnel Motor ccPAS. Funnel plot of raw effect sizes (Hedges' g) versus inverse standard error in the Motor ccPAS meta-analysis. Black circles represent effect sizes included. The contour-enhanced funnel plots display the significance of the effects from in this meta-analysis relative to their magnitude and precision. For estimates falling inside the white and light-blue region, the null hypothesis of null effect can be rejected at the 1 % significance level ($p<0.01$) and 5 % ($p<0.05$) respectively. For estimates in darker-blue regions, significance is above 5 % and 10 %.

estimate of the overall effect obtained from PET-PEESE procedure gave a corrected estimate resembling the original (g=0.47, p=0.001, CI[0.22 0.73]). P-curve analysis was also used to determine publication bias (Fig. S2), showing the observed p-curve versus null effects and sufficient power. We found that of the total 65 effects provided, 38 presented significant findings (58.46 %). The evidential value, or the true effect size, was found to be present, indicating that these findings are unlikely to be the product of publication bias and p-hacking. Supplementary analyses performed on aggregated data from the studies confirmed the effect size magnitude found in multilevel modelling (Fig. S3).

3.2.2. Subgroup analysis: Brain network

A subsequent subgroup mixed-effect analysis including the moderator of *Brain Network*, which included M1-M1 (k=17); PMv-M1 (k=22); PPC-M1 (k=10); CB-M1 (k=11) and SMA-M1 (k=5), was conducted. The targeted circuit was found to have non-significant influence on effect size ($F(4,16) = 2.09$, $p = 0.13$). This meant that overall effect size was not statistically different across subgroups (see Fig. S4, Table S2), however, a closer inspection of effect size estimates revealed that SMA-M1 ccPAS had the smallest magnitude and produced a non-significant outcome (g= 0.30 [-0.01 0.61], p> 0.05) with its prediction interval intersecting the null value, indicating insufficient evidence [-0.19 0.78].

3.2.3. Premotor-ccPAS meta-analyses

Considering the number of publications, we deemed relevant to conduct a further meta-analysis to closely inspect results from studies targeting the PMv-M1 network (n=12, k=50), focusing on all neurophysiological outcomes of ccPAS administered on PMv-M1 network (CSE, dual-coil TMS, ppTMS). We performed a main meta-analysis to evaluate the effect of PMv-to-M1 protocols, thought to induce LTP-like effects (n= 12, k= 50), and a control analysis on M1-to-PMv ccPAS, which should determine LTD-like effects (n=8, k=17). The studies included in the PMV-M1 and M1-to-PMv meta-analyses tested an overall sample of 279 and 162 participants, respectively.

3.2.4. PMv-to-M1 ccPAS

The pooled average outcome based on the 3-level model for PMv-M1 ccPAS was g= 0.46 (95 % CI [0.33 0.58) with an effect size significantly different from zero ($t(11)=7.91$ $p<0.0001$). The observed outcomes ranged from g=0.038–1.01, and the 95 % prediction interval [0.014 0.89] showed that true effect of the studies was consistent with the estimated average outcome. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Fig. 5. The estimated variance components were $\tau^2_{\text{Level 3}}=0.016$ and $\tau^2_{\text{Level 2}}=0.021$. This means that $I^2_{\text{Level 3}}= 21.47$ % of the total variation was attributed to between-cluster, and $I^2_{\text{Level 2}}= 27.83$ % to within-cluster heterogeneity.

Visual inspection of publication bias using funnel plots suggested no apparent asymmetry in effect size distribution (Fig. 6). Result of multilevel Egger's test confirmed the absence of a significant relationship between effect size and sampling error (p= 0.36, Fig. S5). Adjusted estimate of the overall effect obtained from PET-PEESE procedure gave a corrected estimate stronger than the original (g=0.65, p=0.01, CI[0.16 1.13]). P-curve analysis was also used to determine publication bias (Fig. S6). We found that of the total 50 effects provided, 29 presented significant findings (58 %). The evidential value, or the true effect size, was found to be present, indicating that these findings are likely not the product of publication bias and p-hacking. Supplementary analyses performed on aggregated data from the studies confirmed the effect size magnitude found in multilevel modelling (Fig. S7).

3.2.5. Subgroup analyses: Cognitive State, Tested Cortical Circuit, Timing, PMv-Intensity

One mixed-effect analysis was conducted including the moderator of *Cognitive State*, i.e., Rest (k=34); Task (k=10); ccPAS (k=6). The moderator significantly influences the effect size ($F_{2,47} = 13.39$, $p < 0.001$): specifically, the effect size was found to be reduced when testing at Rest compared to Task (b= 0.28, 95 % CI [0.09 0.47], $p < 0.05$) and ccPAS (b= 0.43, 95 % CI [0.25 0.62], $p < 0.001$) (Fig. 7). Nonetheless, despite different all individual subgroup estimates are significant

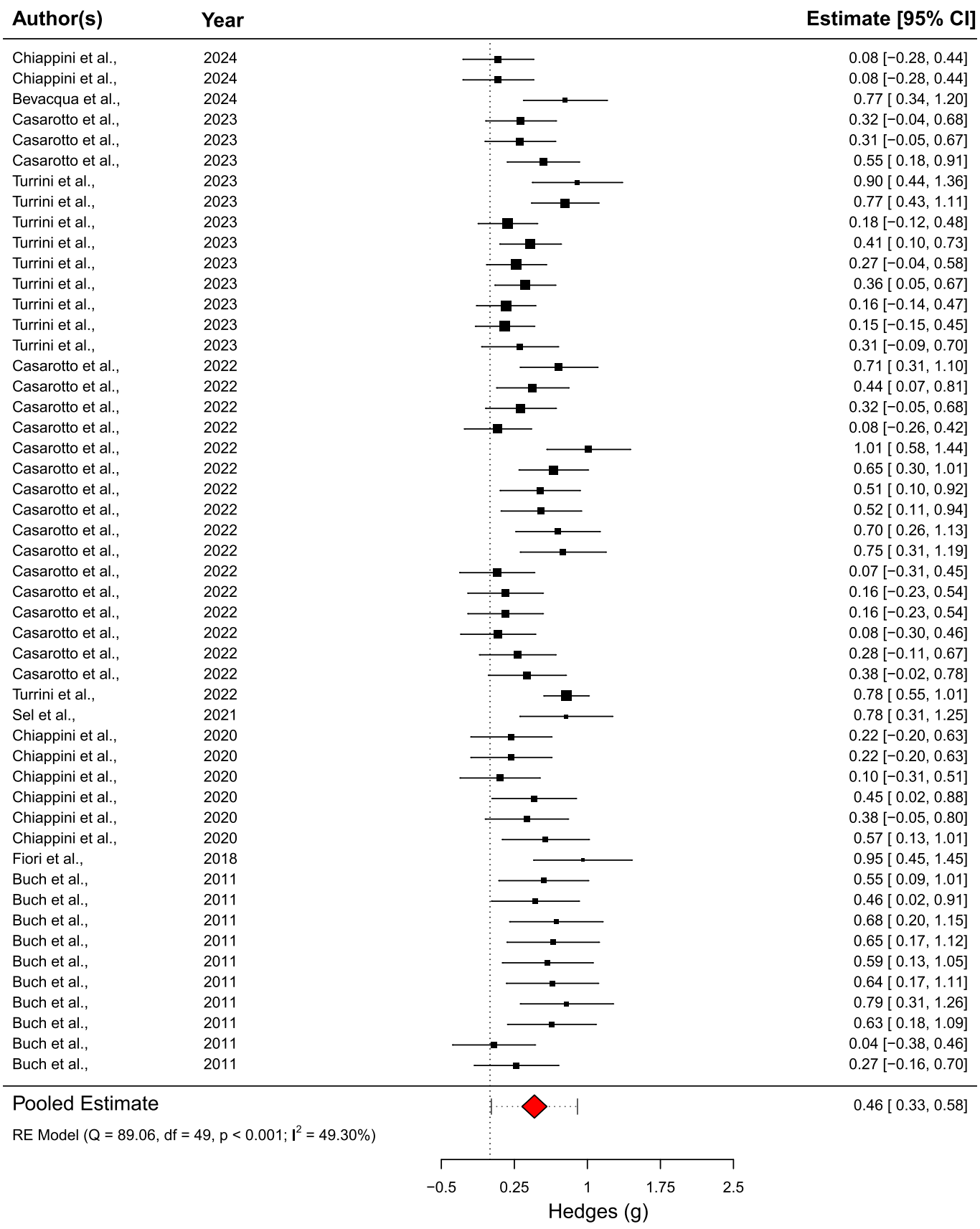

Fig. 5. Forest PreMotor ccPAS. Forest plot of absolute effect sizes (Hedges' g) for all studies included in the Premotor ccPAS meta-analysis. The pooled estimate and 95 % confidence interval (red diamond) is reported with 95 % prediction interval (dashed horizontal line) and compared to null effect (dashed vertical line). The size of each black square indicates the weight of the effect size in the combined analysis with 95 % CI (black lines). Multiple effect sizes are reported for the studies.

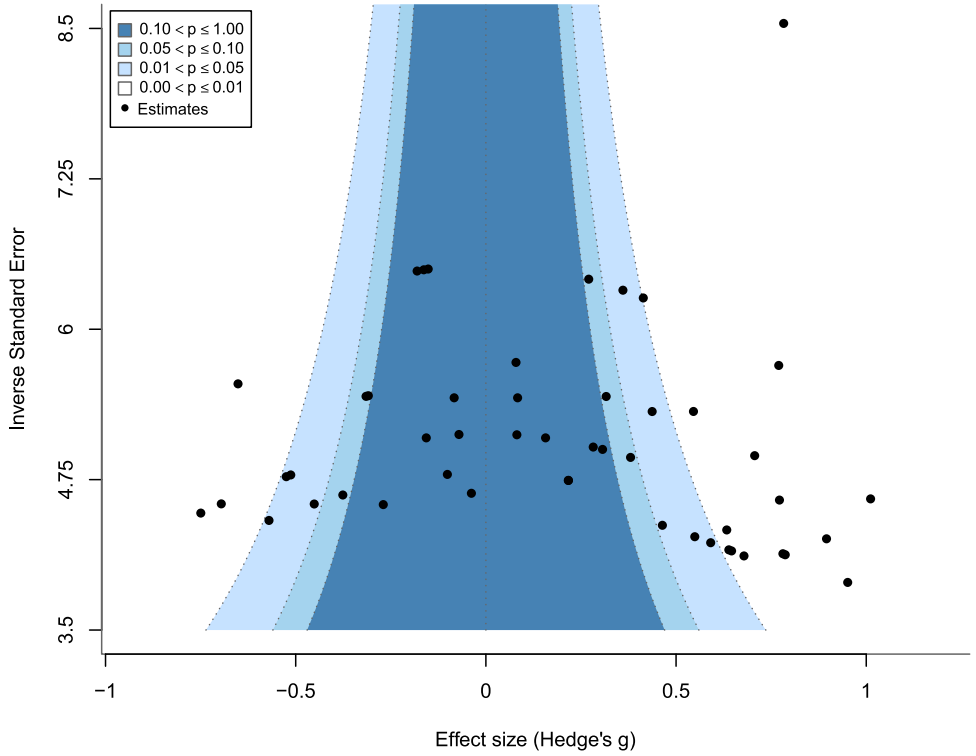

Fig. 6. Funnel Premotor ccPAS. Funnel plot of raw effect sizes (Hedges' g) versus inverse standard error in the Premotor ccPAS meta-analysis. Black circles represent effect sizes included. The contour-enhanced funnel plots display the significance of the effects from in this meta-analysis relative to their magnitude and precision. For estimates falling inside the white and light-blue region, the null hypothesis of null effect can be rejected at the 1 % significance level ($p<0.01$) and 5 % ($p<0.05$) respectively. For estimates in darker-blue regions, significance is above 5 % and 10 %.

(Table S3).

The analysis including the *Tested Cortical Circuit* moderator included the subgroup of Corticospinal (k=17), Premotor (k=21) and Intracortical (k=12) effects. Although non-significant ($F_{2,47} = 2.52$, $p = 0.09$), effect size estimates for each subgroup (Table S4) indicate that only the prediction interval of the effect size of the Premotor circuit does not overlap with a null effect [0.12 0.97].

The analysis including the moderator of *Timing* considered subgroup of sessions until 15 from ccPAS (Post_1, k=30) and following 20 minutes (Post_2, k=20). The *Timing* was found to have non-significant influence on effect size ($F_{1,48} = 1.22$, $p = 0.28$). While both individual estimates of effect sizes appeared significant, the later timing (Post_2) was found to produce less consistent effect sizes (PI [-0.05 0.85], Table S5).

The analysis including the moderator of *Stimulation Intensity* tested the impact of subthreshold (90 %, k=37) vs suprathreshold (110 %, k=13) conditioning of the PMv. The moderator proved non-significant ($F_{1,10} = 0.21$, $p = 0.66$); yet, a narrative difference was observed in the estimates of effect sizes, with suprathreshold conditioning having more variable and potentially less effective outcomes (g=0.42, CI[0.11 0.73]) than subthreshold conditioning (g=0.49, CI[0.31 0.67]). However, the variability of both prediction intervals suggests that more evidence is required (Table S6).

3.2.6. *M1-to-PMv ccPAS*

This control meta-analysis returned a marginally significant low-to-medium effect size (g= 0.36, 95 % CI [-0.002 0.729]) (Fig. S8). The effect appeared to be less robust than the previously reported outcomes on motor networks, opening to possible methodological and theoretical considerations (see supplementary analysis, Fig. S9-12).

3.3. *Probing and measuring activity in the cortical circuits supporting visual perception with ccPAS*

Six studies were identified that investigated the cortical dynamics of the visual cortex with ccPAS. These studies targeted different pathways and visual networks, primarily including the occipital, parietal and temporal regions.

The first study that investigated visual cortical dynamics with ccPAS focused on examining the role of the cortical route connecting the V5/MT+ and V1/V2 areas in motion perception (Romei et al., 2016). The study involved a motion coherence discrimination task to measure the ability to perceive and distinguish coherent motion from random motion. The study investigated whether a ccPAS protocol designed to strengthen the re-entrant (backward) projections from V5/MT+ to V1/V2 (20 ms IPI, Silvanto et al., 2005b) could enhance individual's sensitivity to stimuli in motion. Results show that strengthening the pathway connecting V5/MT+ with V1/V2 results in enhanced sensitivity to coherent motion, which last up to 60 minutes after ccPAS, following a temporal profile consistent with Hebbian plasticity. Specifically, this pattern of results was dependent on the direction and timing of the stimulation; neither V1/V2-to-V5/MT+ ccPAS nor a ccPAS protocol that simultaneously targets the two areas (0 ms IPI) changed motion perception.

Chiappini et al. (2018) followed a similar approach to investigate if it is possible to selectively improve the synaptic efficiency of specific motion-related neural populations with ccPAS. To this aim, participants were exposed to stimuli moving in a specific direction which is thought to engage direction-specific neurons in the V5/MT+ and V1/V2 pathway. While participants observed the stimuli in motion, ccPAS was then applied on the pathway connecting the V5/MT+ and V1/V2 (20 ms IPI, Romei et al., 2016) with the purpose of selectively increase Hebbian plasticity in the neurons encoding motion. The results showed enhanced sensitivity to motion perception when comparing sensitivity ratings

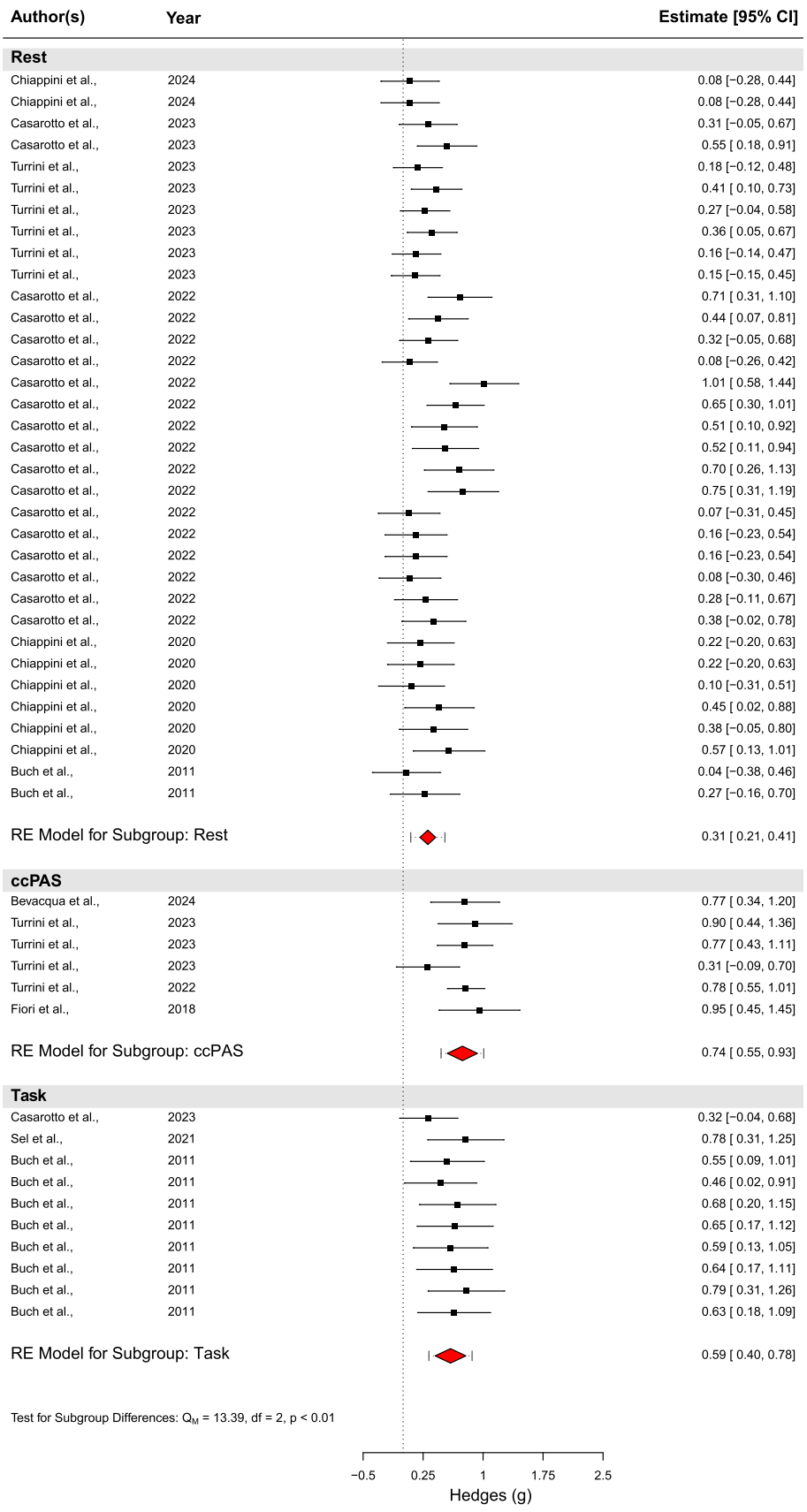

Fig. 7. PreMotor ccPAS moderator. Forest plot distinguishing pooled effects for each Cognitive state considered in the Premotor ccPAS moderator analysis. Effect sizes with 95 % CI (black squares and lines) are grouped depending on the moderator levels (n=3) and compared versus null effect (dashed horizontal line). Random effect estimates for each subgroup are reported with 95 % PI (red diamonds and dashed line).

before and after ccPAS. Interestingly, this sensitivity enhancement was only true when the first pulse was delivered over V5/MT+ and the second pulse was on V1/V2 (*versus* reversed V1/V2-to- V5/MT+ ccPAS), and also only when TMS was applied at subthreshold level (i.e. 80 % of phosphene threshold) (Chiappini et al., 2018).

Di Luzio et al. (2022) further examined the role of the V5/MT+ to V1/V2 pathway on perceptual decisions with ccPAS. Existing evidence suggest that perceptual confidence and accuracy of the decision functionally rely on two separate, but functionally related, networks (Maniscalco et al., 2016; Rahnev et al., 2012). While motion sensitivity in decision making is mostly underpinned by neurons of V5/MT area, decision confidence is sustained by the activity of the inferior parietal sulcus (LIP/IPS). In two separate experiments, the researchers used ccPAS to either strengthen connections from V5/MT+ to V1/V2, or connections in the IPS/LIP-to-V1/V2 pathway, and asked participants to perform a task where they ought to identify the direction of a pattern of dots and to provide confidence ratings on their responses, often referred to as metacognition. Results showed that ccPAS aimed at potentiating the connectivity between the V5/MT+ and V1/V2 improved motion sensitivity inducing a bias in confidence reports, without ameliorating metacognition. On the other hand, stimulation aimed at enhancing connectivity between the IPS/LIP and V1/V2 based on a IPI (30 ms, Parks et al., 2015), relative to control stimulation on the same network (0 ms IPI), increased the efficiency in confidence ratings, improving metacognition without affecting motion sensitivity. These changes lasted up to 30 minutes.

A further study combining ccPAS with EEG revealed that increasing connectivity in the pathway connecting the V5/MT+ to V1/V2 not only improves visual motion perception and increases confidence levels (Bevilacqua et al., 2023a), but also increased backward alpha signals from V5 to the early visual cortex. By contrast, the reversed order of stimulation – i.e., first pulse on V1/V2 and second pulse on V5/MT+, did not lead to any changes. Collectively, these results reveal important evidence of a double dissociation in the visual system whereby decision accuracy is supported by low-level processing in the V5/MT+ - V1/V2 network, and metacognition is instantiated in higher level associative areas in the parietal cortex.

Furthermore, ccPAS was used to systematically assess the network supporting horizontal motion perception in humans Chiappini et al. (2022) in a comprehensive sample of 54 participants. Horizontal motion perception is primarily supported by the transcallosal connections between the left and right V5/MT+ (Rose et al., 2006; Rose and Büchel, 2005). In four separate experiments, the researchers used ccPAS over the left and right V5/MT+ (25 ms IPI as informed by previous evidence on interhemispheric delays between these areas - (Strüber et al., 2014) to manipulate connectivity strength between the two component areas. They then measured horizontal motion perception at four different time intervals: immediately after ccPAS, and then at 30-, 60-, and 90-minutes after ccPAS. Strengthening connections from the left to the right V5/MT+ with ccPAS increased sensitivity to horizontal motion; these changes evolved rapidly and lasted up to 90 minutes. Limited perceptual changes were observed when strengthening connections from the right to the left V5/MT+, suggesting that the interhemispheric connections projecting from the left to the right V5/MT+ (as opposed to the connections from the right to the left V5/MT+) play a particularly important role in integrating local sensory input during horizontal motion perception (Chiappini et al., 2022). Interestingly, modulation of perceptual bias in the direction of horizontal motion mirrored the asymmetrical nature of the projections connecting left and right V5/MT+ in the human visual cortex (ffytche et al., 2000; Morikawa and McBeath, 1992; Strong et al., 2019). This novel finding showing a functional asymmetry in the pathway between the left and right V5/MT+ could only be uncovered by means of ccPAS, which highlights the power of the technique to interrogate neuronal networks.

Recently, a comprehensive study involving 155 healthy participants tested across five experiments investigated the network connecting the posterior Superior Temporal Sulcus (pSTS) and V1/V2 and their role in face perception (Borgomaneri et al., 2023). Borgomaneri and colleagues first estimated the inter-areal communication timing between the pSTS and V1/V2 using a combination of single pulses of TMS and EEG recordings (TMS-evoked potentials). The authors then capitalise on such estimated intra-areal communication timing (~200 ms) to fine-tune their ccPAS protocol and evaluate the impact of strengthening pSTS-V1/V2 connections with this tailored ccPAS protocol. The results show that applying this pSTS-to-V1/V2 ccPAS protocol leads to enhanced visual sensitivity to facial expressions in three distinct experiments. This perceptual increase is paralleled by anincrease in the P1 component of event-related potentials (ERPs) evoked by facial stimuli, which is maximal over the conditioned site (V1/V2). This increased perceptual sensitivity to faces lasts for about 80 minutes, peaking at 40–60 minutes. The effects were found to be dependent on the specific temporal pattern of stimulation, because reversed V1-to-pSTS stimulation or pSTS-to- V1/V2 stimulations with other IPIs (0 ms or 100 ms) did not lead to any changes (Borgomaneri et al., 2023).

3.4. Meta-analysis of ccPAS studies of the visual system

The findings described in the systematic review of ccPAS studies in the visual system were subsequently analysed through a meta-analysis, comprising all studies in which the ccPAS targeted circuits including posterior visual cortices. The "Visual-ccPAS" meta-analysis considered n=6 studies and k=37 effect sizes overall. The studies included tested an overall sample of 175 participants.

The analysis showed that the pooled average outcome based on the 3-level model was g= 0.53 (95 % CI [0.43–0.63) and that such effect size differed significantly from zero (t(5)=13.62 p<0.0001). The observed outcomes ranged from g=0.017–1.17, and the 95 % prediction interval [0.22 0.84] for the true outcomes of the studies indicated the same direction as the estimated average outcome. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Fig. 8. The estimated variance components were $\tau^2_{\text{Level 3}}$=0.013 and $\tau^2_{\text{Level 2}}$=0.001. This means that $I^2_{\text{Level 3}}$= 22.58 % of the total variation was attributed to between-cluster, and $I^2_{\text{Level 2}}$= 0.01 % to within-cluster heterogeneity.

Visual inspection of publication bias using funnel plots suggested no apparent asymmetry in effect size distribution (Fig. 9). Result of multilevel Egger's test confirmed the absence of a significant relationship between effect size and sampling error (p= 0.31, Fig. S13). Adjusted estimate of the overall effect obtained from PET-PEESE procedure returned a corrected estimate stronger than the original (g= 0.69, p= 0.02, CI[0.21 1.17]). P-curve analysis was also used to determine publication bias (Fig. S14), showing the observed p-curve versus null effects and sufficient power. We found that of the total 37 effects provided, 28 presented significant findings (75.68 %). The evidential value, or the true effect size, was found to be present, indicating that these findings are unlikely the product of publication bias and p-hacking. Supplementary analyses performed on aggregated data from the studies confirmed the effect size magnitude found in multilevel modelling (Fig. S15).

3.4.1. Subgroup analyses: Timing

Mixed-effect analysis including the moderator of *Timing* which included results obtained within 15 minutes from ccPAS (Post_1, k=13); between 20 and 60 minutes (Post_2, k=19) and extending after 80 minutes (Post_3, k=5). The moderator was found to have non-significant influence on effect size ($F_{2,34} = 0.16$, $p = 0.86$).

Estimates of effect sizes for each subgroup appeared significant, even considering an apparent decrease of effect size magnitude and robustness with the time elapsed from ccPAS administration (i.e., Post_3, Table S7).

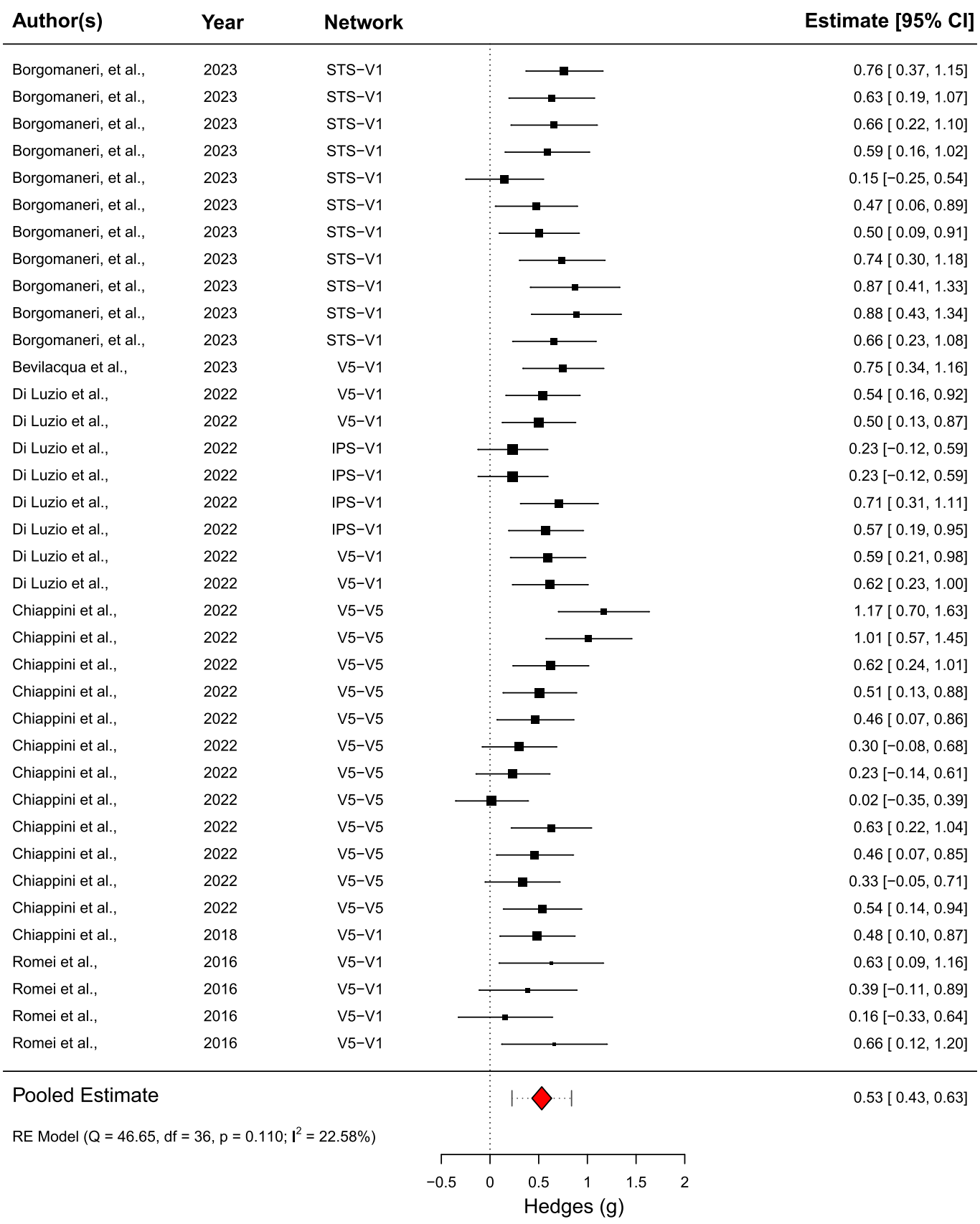

Fig. 8. Forest Visual ccPAS. Forest plot of absolute effect sizes (Hedges' g) for all studies included in the Visual ccPAS meta-analysis. The pooled estimate and 95 % confidence interval (red diamond) is reported with 95 % prediction interval (dashed horizontal line) and compared to null effect (dashed vertical line). The size of each black square indicates the weight of the effect size in the combined analysis with 95 % CI (black lines). Multiple effect sizes are reported for the studies.

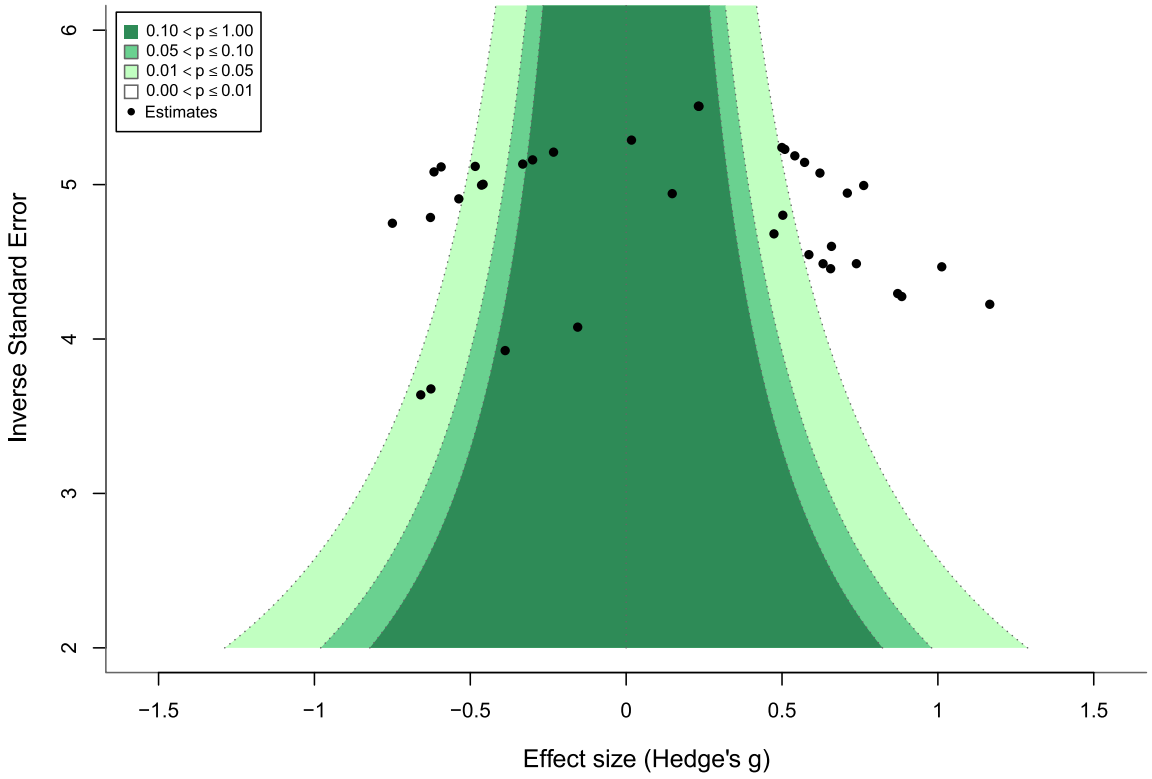

Fig. 9. Funnel Visual ccPAS. Funnel plot of raw effect sizes (Hedges' g) versus inverse standard error in the Visual ccPAS meta-analysis. Black circles represent effect sizes included. The contour-enhanced funnel plots display the significance of the effects from in this meta-analysis relative to their magnitude and precision. For estimates falling inside the white and light-green region, the null hypothesis of null effect can be rejected at the 1 % significance level ($p<0.01$) and 5 % ($p<0.05$) respectively. For estimates in darker-green regions, significance is above 5 % and 10 %.

3.5. Examining the prefrontal networks that support executive functions with ccPAS

We identified 9 studies that examined high-order cognitive processing in the prefrontal and fronto-parietal networks with ccPAS. Due to the variability in the definition of the targeted cortical regions and in the studied outcomes, we acknowledged a meta-analytic approach not to be appropriate in this instance. In this section we provide a systematic review of the findings.

ccPAS was first used over prefrontal regions to assess the functional role of the fronto-parietal network involving the dorsolateral prefrontal cortex (DLPFC) and the PPC in memory and attention processes (Casula et al., 2016). This study combined ccPAS over the two component areas with EEG recordings and showed enhanced amplitude of the TEPs recorded over the DLPFC when contrasting amplitudes before and after DLPFC-to-PPC ccPAS. By contrast, when reversing the order of the pulses – i.e., first pulse over the PPC and second pulse on DLPFC, the TEPs amplitude recorded over DLPFC decreased. These changes are consistent with the principles of LTP and LTD, showing that increasing or decreasing synaptic plasticity with ccPAS in the pathway connecting the DLPFC with the PPC, leads to increases or decreases of DLPFC cortical excitability (Casula et al., 2016).

Furthermore, Santarnecchi et al. (2018) tested whether ccPAS targeting connections between areas of the default mode network (DMN) and the task-positive network (TPN) could result in the alteration of their functional connectivity as measured with fMRI. Activity in the DMN and the TPN are typically anticorrelated; this means that when DMN activity enhances, TPN activity decreases (Fox et al., 2005). The results of this study demonstrated that increased coupling between a left prefrontal site of the TPN and a left parietal site of the DMN with ccPAS (10 ms IPI) partially reversed the inverse activity pattern between the two areas. This is, when contrasting the functional connectivity measures before and after ccPAS, DMN activity increases tended to co-occur more often with increases in TPN activity. This was particularly true for participants who showed a weak inverse relationship in baseline activity between the two component areas. Changes in functional connectivity between the DMN and the TPN were also observed during an attention task, where participants there was a faster switch between rest and task states following ccPAS (Santarnecchi et al., 2018).

Kohl et al. (2019) used ccPAS to manipulate connectivity in the route connecting the right inferior frontal cortex (IFC) with the right pre-supplementary motor area (pre-SMA). The network involving the IFC and pre-SMA is thought to be important for inhibiting or withholding motor responses that are no longer relevant or appropriate in an ever changing environment (Aron et al., 2007). This process is referred to as response inhibition and it is often measured by the stop signal task (SST), whereby participants ought to press a button in response to a 'Go' stimulus and have to withhold their prepotent responses to sudden 'Stop' stimulus (Aron, 2011). Enhancing connections between the pre-SMA and the rIFC with ccPAS led to significant changes in task performance, which were also influenced by age: younger individuals (18–25 YO) showed reduced ability to inhibit responses when pre-SMA was stimulated before rIFC with a 10 ms IPI. Conversely, older participants (aged 25–39) showed improved response inhibition when rIFC was stimulated before pre-SMA with a 4 ms IPI (Kohl et al., 2019). The latter results were replicated in a subsequent study by Mandali and colleagues (Mandali et al., 2021) who identified that stimulating the rIFC before the pre-SMA with 4 ms IPI ccPAS could improve response inhibition in older adults. They also showed an increased inhibition ability in younger adults when enhancing the rIFC-to-pre-SMA pathway, but the greatest effect was observed in the older adults.

Activation in both the right and left lateral prefrontal cortex (PFC) are associated with different emotional responses: while left PFC activity is related to approaching responses, activity in the right PFC is linked to

avoidance behaviours (Harmon-Jones et al., 2010). It is argued that altered connectivity between the left and the right PFC can explain cognitive and affective impairments (Hoppenbrouwers et al., 2014; Sutton and Davidson, 1997). Zibman et al. (2019) tested this hypothesis by manipulating transcallosal connections between the left and right PFC and measuring activity changes in these two areas with TEPs (Zibman et al., 2019). The results show that stimulating the left-to-right PFC pathway with ccPAS results in increased attentional bias in an emotional reactivity task alongside amplitude increases in the TEPs in the right PFC. Conversely, right-to-left PFC ccPAS stimulation was linked to a decrease of attentional bias in the task – although it also leads to TEP amplitude increases in the left PFC indicating increased inter-hemispheric signal propagation in the direction of the paired stimulation. This suggest that ccPAS is a suitable approach to investigate, and perhaps ameliorate, symptoms associated with affective disorders.

Moreover, Nord et al. (2019) aimed to investigate the role of the network involving the lateral PFC and the intraparietal sulcus (IPS) in decision-making strategies with ccPAS (Nord et al., 2019). They manipulated neural plasticity and connectivity by applying ccPAS over PFC and IPS and examined the effects on decision making and working memory. Strengthening the connections from the IPS to PFC with ccPAS (10 ms IPI) changed decision-making styles by making them more goal-directed. By contrast, reversing the order of stimulation (i.e. PFC-to-IPS ccPAS) did not induce any changes in decision-making. Similarly, adopting a ccPAS protocol with an IPI that is not compatible with the Hebbian-like principles of pre-and-postsynaptic activations for this network (i.e. 100 ms IPI) did not change decision-making styles. Additionally, no modulations in working memory performance were observed. These findings highlight the potential of utilising ccPAS in decision-making, but more research in both healthy individuals and those with decision-making disorders is required.

The construct of fluid intelligence (gf) and its underpinning network was also explored with ccPAS. Amongst the cortical areas supporting gf, the left inferior parietal lobe (IPL) and left middle frontal gyrus (MFG) are believed to be crucial for gf based on cognitive models (Santarnecchi et al., 2017). Momi et al. (2020) tested whether increasing functional coupling between these two cortical areas would lead to increased performance in the Sandia matrices, a Raven-like task that measures logical and relational reasoning (Matzen et al., 2010). The authors show that increasing connectivity between the IPL and the MFG with ccPAS (10 ms IPI) improved accuracy and decreased response times for logical reasoning. Conversely, reversed MFG-to-IPL ccPAS (10 ms IPI) improved accuracy and decreased response times for relational reasoning (Momi et al., 2020). These results show a double dissociation between task and direction of the connections, whereby the parietal-to-frontal pathway supports logical reasoning while the pathway connecting the frontal with the parietal areas is linked to relational reasoning.

In line with previous investigations showing a direct link between the strength of synaptic plasticity and the functional connectivity measured with EEG coherence between two cortical areas (Trajkovic et al., 2023), Hooyman and colleagues demonstrated that ccPAS over the right PFC and the right M1 (5 ms IPI) also leads to increases in EEG coherence in the high range of the beta band between the two areas (Hooyman et al., 2022).

Finally, one recent publication used ccPAS to manipulate connectivity between the frontal eye field (FEF) and the IPL (Guidali et al., 2023), with the goal of modifying the phenomenon of pseudoneglect in healthy young individuals. The results showed that FEF-to-IPL ccPAS (10 ms IPI) reduced pseudoneglect, while the opposite IPL-to-FEF ccPAS or the use of a different inadequate IPI (100 ms) did not lead to changes. Authors discuss that the effect may be ascribed to an increased top-down attentional control spurred by enhanced fronto-parietal connectivity and conclude that ccPAS holds potential as a rehabilitation protocol in patients suffering from severe visuospatial pathologies.

4. Discussion

In this systematic review, we summarised 41 articles that capitalise on advanced non-invasive neuromodulation protocols, namely ccPAS, to investigate cortical dynamics in the human brain. Moreover, we aimed to provide a meta-analysis of the effect size of ccPAS interventions, complemented by the inclusion of relevant moderating factors which we hope it will be useful guidance for future interventions. Our results suggest that the ccPAS protocol is an effective way to transiently manipulate cortico-cortical connections between two targeted areas following the principles of STDP. Such connectivity alterations result in changes to the functional influence that one cortical area exerts over another anatomically connected one which, in turn, modify the neurophysiological and behavioural outputs of the circuit.

Our meta-analysis includes studies centred on two main cortical networks: the motor control network and the visual network. We focused on these two networks because we felt there were enough published studies investigating these networks to ensure good statistical reliability. The results illustrate that ccPAS protocols are consistently effective in changing connectivity strength between the nodes of a given cortical network. Those connectivity changes are associated with a reliable medium effect size. The combination of multivariate reporting in primary studies and the absence of small-study bias in our meta-analyses suggest that the presented effect sizes likely approximate true effects. To our knowledge, this meta-analysis represents the first attempt to quantitatively assess the effects of ccPAS in the human brain, whilst also complementing previous systematic reviews with novel and significant research publications (Guidali et al., 2021b, 2021a; Hernandez-Pavon et al., 2023a, 2023b).

4.1. Examining the reliability of the ccPAS protocol to investigate motor control networks

Most of the ccPAS studies investigate pathways comprising M1, which often contrast changes in CSE measured before and after manipulating connectivity between the M1 and another motor control area that is functionally relevant and anatomically connected to M1. Therefore, it is possible to estimate the joined efficacy of the ccPAS protocol across all these studies by focusing on CSE changes that occur as the result of manipulating cortico-cortical connections with ccPAS. It is important to note that while some motor areas connecting to M1 have a faciliatory effect on CSE, the functional influence of some other areas can inhibit motor-related M1 CSE. To address this, all effect sizes included in this meta-analysis were normalized to their absolute values.

The main estimate, which included five main motor pathways (PPC-M1, CB-M1, PMv-M1, SMA-M1, M1-M1) denoted a medium effect size. If each of these pathways was considered separately, the pattern of results would exhibit slight variation. This is, a medium-to-high effect size was obtained for the CB-M1 pathway, a medium estimate for the PPC-M1, M1-M1 and PMv-M1 circuits, whereas SMA-M1 provided a less consistent effect size. The effects of the ccPAS on the M1-SMA circuit appear different from other pathways according to the findings reviewed here (Arai et al., 2011; Bevacqua et al., 2024). This could indicate that different intervals between pulses are required to elicit pre-and post-synaptic activity in the SMA-M1 circuit depending on the direction of the stimulation – SMA-to-M1 versus M1-to-SMA. Further investigations are required to test this hypothesis. However, it is worth noting that there is a limited number of studies that have focused on the pathway connecting SMA to M1, and the route connecting CB to M1. Therefore, we ought to be cautious in interpreting the estimates of efficacy computed on studies that focused on these two networks.

Some stimulation parameters were not included as moderators of the analysis, particularly the IPI and the stimulation intensity used to target the two cortical sites. Different studies adopted different IPIs, based on the unique, temporal dynamics of each network, and different stimulation intensities adjusted to the targeted pathway and in line with the

methodological approaches taken in previous literature. Thus, we believe it would have been inappropriate to use these two variables as moderators of the main meta-analysis of all motor studies, but we acknowledge that their exclusion may be a limitation of the present work. Yet, several moderators were included in the specific analysis that focused on the PMv-M1 pathway.

4.2. Investigating the effectiveness of ccPAS in changing PMv-M1 connectivity and M1 cortical excitability

A good deal of studies has focused on investigating the cortico-cortical dynamics of the pathway involving PMv and M1. For the purpose of our meta-analysis, we have focused on the studies that measured neurophysiological aftereffects resulting from increasing PMv-M1 connectivity. In line with the notion that the PMv exerts a state dependent effect over M1 (Davare et al., 2011, 2009, 2008), we found that the efficacy of the ccPAS protocol over the PMv-M1 route is also effectively modulated by the state of the participant. Specifically, the magnitude of the effect size tends to be smaller when participants are tested at rest compared to when they are tested during action performance, and also when tested during terminal phases of the ccPAS protocol, concurrent with the emergence of plasticity effects in the stimulated pathway (Bevacqua et al., 2024). The greater effect sizes observed when examining the ccPAS influence on CSE during action performance may indicate that ccPAS over the PMv-M1 pathway is particularly effective for the neurons involved in motor execution (Sel et al., 2021).

In a second analysis, we probed which neurophysiological outcome metric is most sensitive to PMv-to-M1 ccPAS manipulations. Although differences between the metrics were not significant, we observed a trend indicating that effective connectivity as probed with dual-coil TMS seems to be most sensitive to ccPAS manipulations, showing a medium-to-high effect size. By contrast, M1 CSE probed with spTMS and intracortical protocols (i.e., SICI, SICF, ICF) provided smaller effect size estimates. The pre-eminent efficacy of dual-coil effective connectivity protocols is unsurprising, as this technique provides the most direct readout of manipulations of cortico-cortical connectivity through TMS.

We also tested two other moderators; namely the time elapsed since the end of ccPAS protocol and the PMv stimulation intensity. These did not show significantly relevant effects. However, the descriptive report suggested that the magnitude of the ccPAS effects is stronger when tested right after the ccPAS protocol, as opposed to at later times. It might be difficult to interpret the time course of effects following ccPAS. This is because studies have employed various outcome measures, often assessed at different time points. This inconsistency in measurement timing across studies could introduce variability in the observed delays relative to stimulation. While we implemented sensible time windows to address this concern, the analysis of the temporal evolution of the effects might still be impacted.

It is worth noting that most of the studies investigating the PMV-M1 pathway have used an IPI of 8 ms, although some have adopted an IPI of 6 ms. Given the low number of studies adopting a 6 vs 8 ms IPI, it was difficult to consider this factor as moderator in our analysis. Nevertheless, the evidence suggests that both 6 and 8 ms IPI are proven effective to test PMv-M1 interactions (Davare et al., 2008; Lemon, 2012; Sel et al., 2021). Therefore, we suggest that a significant difference is unlikely to emerge when formally testing across studies the effects of ccPAS on the PMv-M1 with 6 ms as opposed to 8 ms in young adults (i.e, < 50 years). However, difference may start to emerge in the elderly brain when taking into account motor network connectivity (e.g., Goldenkoff et al., 2021), suggesting that characteristics of synaptic transmission might be altered (Chiappini et al., 2024a). This hypothesis is yet to be systematically tested in ccPAS.

Indeed, it is yet unclear if older adults preserve some degree of neural plasticity allowing for increases in cortico-cortical connectivity after ccPAS. As argued by Turrini and colleagues (Turrini et al., 2023a), the lack of motor control changes after the PMv-to-M1 ccPAS intervention may be explained by an age-related change in the precise interval to evoke synchronous pre- and postsynaptic activity in the PMv-to-M1 pathway – i.e., 6–8 ms (Davare et al., (2009,2008); see also (Chiappini et al., 2024a; Turrini et al., 2023a). Precise inter-pulse timing is critical if both PMv and M1 TMS pulses are to produce coincident influences on corticospinal activity. It is possible that the decreased white matter integrity often observed in ageing may have lengthen the interval to evoke synchronous activity between PMv and M1 in the elderly brain, and therefore a longer inter-pulse timing should be applied. This could also explain the disparity in age group found by Kohl and colleagues (Kohl et al., 2019) when investigating the network connecting the rIFC with pre-SMA. The use of ccPAS as a tool to induce plastic changes in the elderly brain merits further investigation.

Lastly, PMv-to-M1 ccPAS, designed to induce LTP in the circuit, was found to be more effective than the reverse order of stimulation, i.e., M1-to-PMv ccPAS, designed to induce LTD. Indeed, the analysis conducted on the CSE changes before and after the reverse M1-to-PMv ccPAS protocol prove a small effect size which was highly susceptible to sensitivity analysis, suggesting a real effect very close to null values. As a general rule, most ccPAS studies reviewed in this manuscript have adopted the same IPI to control for the direction of the paired associative stimulation; that is, in both PMv-to-M1 and M1-to-PMv ccPAS conditions the IPI is generally kept constant. Because the primary endpoint of all studies was to reproduce LTP-like effects, the IPI tends to be studied and selected to be suitable to induce LTP. However, the same IPI may not be optimal to induce LTD when reversing the order of the paired pulses, a phenomenon that has been extensively observed in animal models (Markram et al., 2011). Therefore, further evidence is needed to accurately assess the effectiveness of the ccPAS protocol leading to LTD.

4.3. Examining the effectiveness of the ccPAS protocol to investigate the cortical networks supporting visual perception

The impact of the ccPAS protocol on visual cortical networks is often assessed using perceptual performance measures during visual sensory tasks. Most of these studies implicate V1/V2 alongside anatomically connected areas that are functionally relevant to V1/V2, such as the V5/MT+ (Bevilacqua et al., 2023a; Romei et al., 2016a), the IPS (Di Luzio et al., 2022), and the pSTS (Borgomaneri et al., 2023). Whereas only one study focused on areas outside V1/V2, targeting bilateral V5/MT+ (Chiappini et al., 2022). Our meta-analysis showed that strengthening cortico-cortical connections in the visual perception network leads to change in perceptual ability and that the magnitude of these changes are associated to a medium effect size characterised by very modest heterogeneity. In contrast to the high heterogeneity found in the estimates in motor control studies using ccPAS, the low heterogeneity that characterises the medium effects reported in ccPAS studies assessing the visual cortex may suggest a greater efficacy of ccPAS in manipulating visual pathways. It is also possible that the behavioural estimates measured in such visual studies are more consistent in nature than neurophysiological measures like CSE. Either way, we should note the variability in the stimulation parameters used in the motor *versus* the visual studies, which make this comparison challenging.

In addition, we assessed the temporal dynamics of the changes deriving from the ccPAS manipulation by comparing the effect sizes recorded at different times after the ccPAS intervention. We did not find any significant moderation of the effect of timing on effect sizes, with all the estimates floating around a medium effect size and only a slight decrease in effectiveness for later times (i.e., over 80 minutes from ccPAS).

4.4. Future perspectives of ccPAS applications

Despite the remarkable scientific work devoted to understanding the impact of ccPAS in cortical networks, the exact mechanism by which ccPAS acts on synaptic plasticity and subsequently alters cortical

connectivity, along with the factors determining this impact, remain unclear. For example, ccPAS is often delivered at rest. But it is possible that delivering ccPAS during a task – i.e., while the targeted network is intrinsically activated, may potentiate connectivity changes (Goldenkoff et al., 2023; Sack et al., 2024; Turrini and Avenanti, 2023). Support for this hypothesis comes from a study showing selective increased sensitivity for a specific motion direction in a visual task resulting from delivering ccPAS during the presentation of motion in the same specific direction (Chiappini et al., 2018). In this line, changes in cortico-cortical connections in the motor control network resulting from ccPAS appear state-dependent, proven by divergent effects in excitability during a grasping task and rest (Buch et al., 2011). On the other hand, the effects of ccPAS do not change if this is delivered immediately after a motor tasks as opposed to after a rest period, which suggests a lack of priming effects on ccPAS efficacy (Turrini et al., 2022). This contrasts with previous evidence (Iezzi et al., 2008) showing that actions executed prior to certain rTMS protocols (i.e. theta-burst stimulation) can alter the impact of the neurostimulation protocol. Therefore, further investigation is needed to determine the state-dependent effects of ccPAS on cortical networks.

Another important aspect that merits attention concerns the stimulation parameters and the dosage of ccPAS. Specifically, the intensity of the TMS stimulation, i.e., the percentage of resting or active M1 motor threshold (MT) or phosphene threshold (PT) that is used to deliver ccPAS. For instance, some studies investigating the PMv-M1 network use 110 % of the resting MT (Buch et al., 2011; Johnen et al., 2015; Sel et al., 2021), whereas other studies employed 90 % of the resting MT (Chiappini et al., 2020; Fiori et al., 2018; Turrini et al., 2023a). Furthermore, studies centred on the visual networks often use higher intensities (~65 % of maximum stimulator output, MSO) (Chiappini et al., 2022; Di Luzio et al., 2022; Romei et al., 2016a), although PT has been employed when state-dependent ccPAS protocols have been employed (Chiappini et al., 2018). Dual-coil TMS studies on effective connectivity consistently demonstrate that the intensity of the conditioning pulse delivered on a cortical area strongly determines activity changes in the anatomically connected area (Bäumer et al., 2009; Civardi et al., 2001). More recently, E-field modelling has emerged as a promising technique that may contribute to the estimation of tailored stimulation intensities, especially when it comes to the study of non-motor cortices (Caulfield et al., 2024; Lynch et al., 2022; Saturnino et al., 2019; Stokes et al., 2005; Thielscher et al., 2015). Relevant stimulation parameters are also the frequency, number, and interval between the paired pulses, which can affect the Hebbian-like plasticity changes observed following the ccPAS intervention. While different ccPAS studies have used different number of pulses – between 90 and 180 dual-coil paired pulses, different frequencies ranging between 0.05 and 0.25 Hz, and sometimes different IPIs to target the same cortical network (e.g., studies investigating the M1-M1 or pSTS-V1 routes), it remains unknown whether the choice of stimulation frequency, pulse number and IPI, can modulate ccPAS related changes. Moreover, the cumulative effects of ccPAS over a number of sessions, and the length of these effects are additional aspects that require investigation. Studies involving multiple sessions or days of stimulation are needed to address this important question. To date, only one study shows long-lasting effects of ccPAS over the PMv-M1 network at 24 h after the intervention (Lazari et al., 2022); while a very recent work from Vesia and colleagues demonstrates the multi-dose effects of repeated within-day sessions of ccPAS targeting the PPC-M1 pathway (Goldenkoff et al., 2024).

Further limitations of the ccPAS research refer to the small sample sizes adopted by some of the studies, particularity when considering the earlier investigations. Although we have now made evident that the impact of ccPAS is associated with a medium effect size, it is crucial for the reliability and the replicability of findings that studies are well-powered. In addition, we note some practical limitations of performing ccPAS studies in the laboratory. While ccPAS offers an excellent opportunity to examine cortico-cortical interactions, this would not apply to areas that are anatomically adjacent (e.g., right M1 and right S1) simply because it is physically impossible to place standard TMS coils targeting the two areas accurately. Moreover, while small coils can be used to target areas that are anatomically close to one-another, smaller TMS coils tend to overheat faster than bigger coils; if the stimulation intensity is high (e.g., over 75 % of MSO), this can lead to an overheating of the TMS coil which could jeopardise completing the full ccPAS protocol. Current protocols are being developed to overcome the limitations related with the spatial configuration of the coils. For example, novel dual-coil TMS setups with overlapping stimulators offer an innovative method to stimulate two adjacent brain regions, overcoming previous technical and spatial constraints (Groppa et al., 2012a, 2012b; Heemels et al., 2024; Hehl et al., 2024). Moreover, new protocols that stimulate multiple areas at different times and intensities such as multi-locus TMS (Koponen et al., 2018; Nieminen et al., 2022) and multichannel TMS array (Navarro de Lara et al., 2023) may contribute to develop new multi-sites ccPAS protocols.

A promising avenue to overcome some of the aforementioned limitations involves combining ccPAS with neuroimaging techniques to help tailoring the ccPAS stimulation parameters via information-based approaches (Romei et al., 2016b). For example, Borgomaneri and colleagues (Borgomaneri et al., 2023) combined spTMS and EEG to accurately examine the inter-areal communication timing in the visual cortex and then tailored the IPI for their ccPAS protocol accordingly. Following the same approach, one could measure the specific EEG frequency rhythms governing a cortical network, and in turn, adapt the interval between the two ccPAS pulses to mimic the intrinsic rhythmic interactions between the two targeted areas. In the same line, structural measures of connectivity – as measured by MRI diffusion tensor imaging, can be used to spatially guide the ccPAS protocol to each individual's specific anatomical connections. In addition to this, dual-coil TMS could be used to determine temporally restricted brain activity coinciding with a movement state to target personalized functional interactions in the motor control network, by constraining the brain state with a behavioural task during ccPAS stimulation (Goldenkoff et al., 2023).

4.4.1. *Translating ccPAS to the clinical settings*

The promise of ccPAS to induce long-term changes in neural circuits in healthy cohorts has sparked interest in its potential therapeutic use. Recent studies suggest that ccPAS may be relevant in treating neurological disorders like Parkinson's disease and psychiatric conditions. Capitalising on the evidence of ccPAS effectiveness to modulate cortical connections in healthy adults (e.g. (Borgomaneri et al., 2023; Buch et al., 2011; Di Luzio et al., 2022; Rizzo et al., 2009; Romei et al., 2016a; Trajkovic et al., 2023; Turrini et al., 2023c; Veniero et al., 2013), recent studies have attempted to investigate altered cortical networks with ccPAS in populations affected by Parkinson's disease (PD) (Di Lorenzo et al., 2018), schizophrenia (SCZ) (Ribolsi et al., 2017), post-stroke symptoms (Bevilacqua et al., 2023b; Rosso et al., 2022) or chronic alcoholism (AUD) (Sallie et al., 2024).

Specifically, studies involving SCZ (Ribolsi et al., 2017) and PD patients (Di Lorenzo et al., 2018) showed reduced changes in cortical plasticity and connectivity resulting from the ccPAS intervention. Similarly, while ccPAS over the rIFC-preSMA route alters inhibitory control in healthy adults, no changes are observed when AUD patients undergo the same protocol (Sallie et al., 2024). These limited or absent neurophysiological and behavioural changes resulting from ccPAS interventions in clinical population could be taken as biomarkers of neurological disorders and to predict clinical outcomes. However, it is worth noting that the abnormal ccPAS after-effects observed in these clinical groups were not related to clinical symptoms. Therefore, further research is needed to assess the potential of ccPAS for diagnosis and treatment design. It is possible that the lack of evident ccPAS effects observed in clinical populations (Di Lorenzo et al., 2018; Ribolsi et al., 2017) can be related to altered mechanisms of STDP in these groups.

Specifically, it may be that the temporal profile supporting cortical communication is altered in patients, and therefore stimulation parameters (e.g., the IPI, frequency or magnitude of stimulation) need to be tailored to effectively engage with their altered brain dynamics.

In addition, ccPAS may be used as an interventional tool for the treatment of neurological diseases. Repeated sessions of ccPAS on cerebello-motor (CB-M1) pathway, coupled with physiotherapy, are able to promote upper limb motor functions and plasticity after stroke (Rosso et al., 2022). Also, preliminary results from Bevilacqua (2023) on the V5/MT+-V1/V2 pathway show some initial evidence of improved motion perception in post-stroke hemianopic patients resulting from ccPAS. Interestingly, recent clinical studies have used a modified version of the ccPAS protocol where ccPAS was delivered with high frequency targeting frontal and parietal areas to treat patients with generalised anxiety disorder (GAD) (Lin et al., 2020; Wang et al., 2022) and PD patients (Fricke et al., 2019). One of these studies reported adverse effects in the patients such as headaches and worsening of the anxiety symptoms. Critically, the parameters and dosage of these interventions may have increased the risk of these adverse events, and they cannot be directly compared with the standard ccPAS protocols. Further pre-registered clinical trials are currently being developed to understand the real clinical potential of the ccPAS technique (Cinnera et al., 2023; Duan et al., 2022; Zhang et al., 2023). To develop translational applications, it is crucial that ccPAS is deemed safe for clinical use. To date, none of the studies included in our review have reported any adverse effects associated with ccPAS, although such studies only involved ccPAS delivered in one single day. The safety aspect of ccPAS should therefore be carefully inspected prior to consider ccPAS in the clinical settings (Rossi et al., 2021). Note that most non-invasive brain stimulation techniques induce short-lived effects lasting under an hour (Huang et al., 2005), and therefore require several administrations which extend over weeks to achieve clinical benefits (Carpenter et al., 2012). In contrast, ccPAS appears to offer a favourable balance between the number of stimulation and the duration of its effects. This potentially implies fewer treatment sessions to obtain beneficial results, highlighting the strong translational potential of ccPAS for clinical application.

4.5. *Limitations of the study*

An important limitation of our work relates to the assumption that ccPAS engages Hebbian STDP mechanisms following the principles of associative plasticity in polysynaptic cortical pathways. Although this assumption is common to most ccPAS studies, the lack of cellular evidence supporting the Hebbian nature of the changes resulting from ccPAS protocols limits the interpretation of the results and leaves the underlying mechanisms of ccPAS open to question. Moreover, we recognize that most ccPAS studies lack a clear definition of the structural pathways they aim to manipulate, and only a few provide direct physiological justifications for the selection of stimulation parameters, particularly in the case of the IPIs. Future research should prioritise providing explicit rationale for parameter choices to enhance the interpretability and consistency of PAS-based studies.

In addition, while most results demonstrated robust, cross-network, plastic effects of ccPAS compared to a null control, moderator analyses rarely achieved significance when employed to examine heterogeneity. Moreover, the inability to systematically investigate how ccPAS effects evolve over time, combined with insufficient evidence for additional categorical moderators, restricts our interpretations. For instance, factors as gender, age, intensity of single-pulse TMS for MEPs measurement, and IPIs that may impact ccPAS outcomes could not be considered. Similarly, the meta-analysis did not include prefrontal networks due to the heterogeneity of the studies, and the inability to quantify the impact of ccPAS on specific neuroimaging measures (e.g., EEG, fMRI). Despite these limitations, the growing body of evidence supports the effectiveness of ccPAS in modulating neural plasticity in healthy cohorts.

5. Conclusion

Here we present a systematic review and meta-analysis assessing the efficacy of the ccPAS protocol to investigate cortical networks. Our meta-analysis provides the first quantitative synthesis of the effects of this protocol and demonstrates the efficacy of ccPAS as a tool for modulating various cortical circuits. The findings reveal that applying ccPAS over motor and visual networks induces neurophysiological and behavioural changes with a positive medium effect size. Moreover, our study offers valuable insights into how methodological factors might modulate the magnitude of ccPAS effects.

Further research is needed to gain a deeper understanding of the mechanisms governing ccPAS and to establish protocols for clinical applications. Moreover, the exploration of individual variability in response to ccPAS and the potential factors influencing its effectiveness will be crucial in tailoring the intervention to specific patient populations. These investigations could pave the way for personalized and effective neuromodulation strategies. Nonetheless, we hope our results showcase the potential of the ccPAS technique to investigate neural cortico-cortical interactions in the human brain. In conclusion, the reports show improvements in neurophysiological, behavioural and cognitive functions using ccPAS, highlighting its potential as a valuable therapeutic tool in the field of neurorehabilitation. As research continues to unfold, the translation of ccPAS from experimental settings to clinical practice holds promise for enhancing patient outcomes and quality of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105933.

Data Availability

The research data/code used for this meta-analysis can be accessed via the Open Science Framework: https://osf.io/zyr6e/?view_only=79bb13da82474324bc1975f43adfe0ba

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