Promoting motor recovery after stroke using cortico-cortical paired associative stimulation

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Summary

Stroke is the most prevalent neurological disorder, the primary cause of long-term disability, and the second leading cause of mortality. Post-stroke motor symptoms critically impact and limit stroke survivors' quality of life. Rehabilitation aims to restore motor function by promoting neuroplasticity and neuronal reorganisation. A promising therapeutic approach involves combining non-invasive brain stimulation (NIBS) with activity-based training to enhance neuroplasticity. NIBS are thought to promote the innate neuronal reorganisation of the functionally relevant networks after a stroke. Amongst NIBS techniques, a pioneering method, often referred to as cortico-cortical paired associative stimulation (ccPAS), allows to enhance neuroplasticity in cortical networks. Unlike traditional approaches, ccPAS enables the manipulation of interregional connectivity within specific cortical pathways. In particular, ccPAS can promote synaptic plasticity and connectivity in a functionally relevant cortico-cortical route tailoring the interventions to individual lesion-specific network alterations. In this viewpoint, we propose and critically evaluate the use of ccPAS as a therapeutic tool using upper-limb motor rehabilitation as a primary example, highlighting its potential for post-stroke recovery. We summarise the limited and contrasting evidence supporting the use of ccPAS after a stroke and make suggestions to overcome the current limitations emphasising the need for further future research.

Keywords: Stroke; Upper limb motor rehabilitation; Neuroplasticity; Cortico-cortical paired associative stimulation; Transcranial magnetic stimulation

Introduction

Stroke is the most prevalent neurological disorder in adults, representing the primary cause of long-term disability and the second leading cause of mortality globally.[1] It causes a range of cognitive and motor impairments that evolve over time and often present simultaneously in a non-systematic, compounded manner. Among these symptoms, lasting functional limitations of the upper limb are particularly common, affecting 55%–75% of survivors.[2] Upper-limb motor impairments lead to a significant underutilization of the affected upper limb, representing a burden to basic activities of daily living, such as feeding and dressing, dramatically impacting stroke survivor's independence and overall quality of life. Here, we discuss a novel neurorehabilitation approach using upper-limb motor recovery as a key example to illustrate its potential for improving clinical outcomes.

Upper-limb motor impairments involve weakness and paralysis arising from disrupted signal transmission from the motor cortex to the spinal cord.[3] These changes impact the generation and timing of muscle contractions and, in turn, affect motor dexterity and movement. Notably, upper-limb motor impairments are often intensified by altered tactile, proprioceptive, and visuomotor integration; abilities needed to identify errors and adapt movements accordingly.[3] Such impairments significantly impact upper-limb neurorehabilitation, often involving reaching and grasping training, which helps to explain the limited efficacy of current clinical approaches, leaving 15–30% of survivors with permanent disability.[1] To improve clinical outcomes, it is paramount to develop interventions that can effectively promote neural plasticity and re-establish the cortico-cortical pathways between visual, sensory, and motor areas.

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Cortical remapping after stroke

Following an ischaemic insult, surviving neural networks initiate a process of spontaneous reorganisation (synaptogenesis) to compensate for the damaged tissue and restore motor output, a process highly dependent on the integrity of the corticospinal tracts.[4] This process starts in the very early stages after the lesion, continues for several weeks, and involves the recruitment of near and distal regions. Thus, soon after a lesion involving the middle cerebral artery, activity in the primary motor cortex (M1) decreases while activation in either premotor or parietal regions increases, depending on the lesion size and location.[5,6] Such overactivation is observed in premotor regions like the dorsal premotor cortex (PMd) and the ventral premotor cortex (PMv) and the supplementary motor area (SMA). These areas are densely interconnected with M1 and share functional properties with M1, including their somatotopic organisation and direct corticospinal projections.[7,8] Premotor regions can assume control over motor functions previously subserved by M1, contributing to adaptive motor behaviour via parallel descending pathways.[9] Thus, animal models show that recovery of dexterity after an M1 lesion is linked to the expansion of PMv and the formation of new corticocortical connections from PMv to the somatosensory cortex (S1).[10] Similarly, patient studies demonstrate increased PMv and PMd activity bilaterally during hand movements,[8,11,12] which are predictive of the degree of motor recovery.[13,14]

Both ipsi-and contra-lesional cortical activations are often observed post-stroke. However, the role of the contralesional hemisphere has been subjected to extensive debate, explained by competing models of cortical remapping involving divergent therapeutic predictions (Fig. 1). The 'interhemispheric competition' model suggests that a stroke leads to excessive inhibition from the healthy onto the damaged hemisphere,[15] implying that non-invasive brain stimulation (NIBS) interventions should focus on disrupting the unaffected hemisphere reinstating interhemispheric equilibrium. However, this view is challenged by evidence showing that the primary change is decreased excitability in the affected hemisphere, with little corresponding hyperexcitability in the contralesional cortex.[16,17] By contrast, the 'vicariation' model proposes that activity in the unaffected hemisphere is likely to reflect the brain's attempt to generate motor output to spinal cord motoneurons via any residual pathway, particularly after larger lesions.[11] This model suggests that NIBS should instead be used to enhance contralesional activations. Lastly, in an attempt to reconcile these two opposing views, the 'bimodal balance-recovery' model posits that in patients with smaller lesions (where more healthy neural areas and pathways can contribute to recovery—i.e., more structural reserve) the interhemispheric competition model better predicts recovery, whereas the vicariation model is more applicable to those with extensive damage (Fig. 1).[18] Taken together, these models highlight the need to tailor NIBS interventions by triaging and stratifying patients based on lesion extent and cortico-cortical connectivity changes.

Potentiating post-stroke cortical remapping with cortico-cortical paired associative stimulation

Although the exact neurophysiological impact of NIBS on neurotransmission and cellular excitability is not yet fully understood, NIBS is thought to modulate synaptic efficacy in glutamatergic and γ-aminobutyric acid-

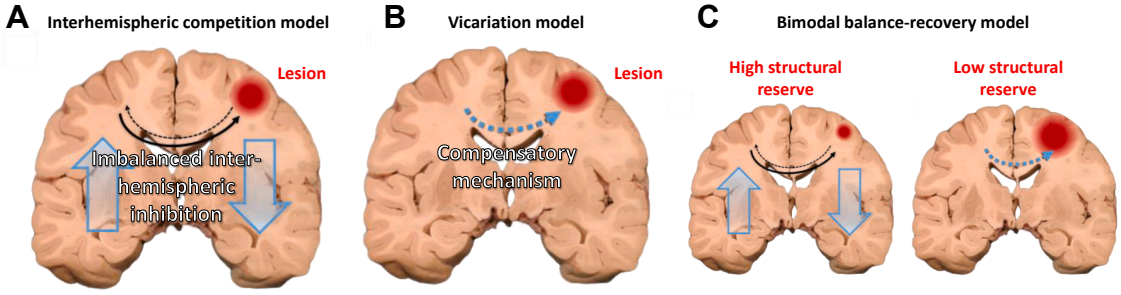

***Fig. 1*: Models of post-stroke cortical remapping. Stroke area displayed in red. A**: Interhemispheric competition model assumes a reciprocal, balanced inhibitory relationship between the hemispheres in the healthy brain. Following a stroke, damage to one hemisphere disrupts this equilibrium leading to excessive inhibition of the lesioned hemisphere by the healthy hemisphere (solid line) and reduced inhibition from the affected side to the healthy side (dashed line). Consequently, the affected hemisphere is considered 'double-disabled,' suffering both from its intrinsic damage and excessive inhibition from the contralateral side. **B**: The Vicaration model suggests that activity in the intact hemisphere contributes to post-stroke functional recovery by 'taking over' the functions lost by damaged areas (light-blue dotted arrow); this process involves functional reorganisation of intercortical connections. **C**: The Bimodal balance-recovery model states that if the structural reserve (i.e., the extent to which neural pathways and relays spared by the lesion contribute to recovery in an individual patient) is high, the interhemispheric competition model can better predict recovery; by contrast, if the structural reserve is low the Vicariation model is more useful in predicting recovery (Di Pino et al., 2014). Brain image is taken from the neuroanatomy website (https://neuroanatomy.ca/coronals.html).

mediated (GABAergic) circuits essential for motor learning,[19] potentiating innate post-stroke neuronal reorganisation.[20] NIBS has been used post-stroke to improve gait, neglect and language symptoms; here we will focus on NIBS on upper-limb rehabilitation.

Amongst NIBS techniques, transcranial magnetic stimulation (TMS) is a key tool used for both prognosis and treatment. For instance, corticospinal tract integrity, assessed by the presence of TMS-induced motor-evoked potentials (MEPs) in the acute stage, is highly predictive of long-term functional outcome.[21] Furthermore, several meta-analyses show moderate efficacy of repetitive TMS in promoting functional recovery,[20,22] particularly when combined with cognitive training[23] or activity-based training.[24] Notably, it is also possible to examine the causal functional influence of one cortical area over another area in post-stroke recovery using paired-coil TMS methods, whereby two TMS coil are placed over two anatomically connected cortical regions.[12] Paired-coil TMS studies have demonstrated that the abnormal increases in interhemispheric inhibition from the contralesional to the ipsilesional hemisphere persists at the onset of attempted contraction of the paretic limb, potentially interfering with movement initiation.[15] Furthermore, other paired-coil TMS studies have probed the physiological influence of contralesional premotor regions, such as the PMd over the ipsilesional M1, revealing that PMd's facilitatory effect on M1 at rest becomes more pronounced following stroke in patients experiencing greater severity.[12] These investigations highlight the potential of paired-coil approaches to target two nodes of the motor control network. By precisely characterising an individual's unique cortico-cortical network alterations after a stroke, paired-coil approaches can inform the design of circuit-based interventions tailored to their specific patterns of interhemispheric imbalance and compensation, and corticospinal tract damage.

Some paired-coil TMS protocols, often referred to as Paired Associative Stimulation (PAS) protocols, involve coupling peripheral nerve stimulation (PNS) over for example median nerve, with a cortical TMS pulse (e.g., on M1) in a repetitive manner.[25] (Fig. 2) PAS is thought to engage mechanisms of spike-timing dependent plasticity (STDP), and its evoked effects have been characterised as Hebbian in nature.[26,27] According to the principles of Hebbian-like STDP,[26] the repeated activation of presynaptic neurons immediately before postsynaptic neurons typically results in long-term potentiation-like changes at the relevant synapses.[27,28] Conversely, when postsynaptic cells fire before presynaptic cells, it often induces long-term depression-like changes. PAS mimics this pre- and post-synaptic neuronal activation by repeated stimulation of two areas in the nervous system. The processes of long-term potentiation and depression are crucial for neuronal reorganisation and strengthening of connections after stroke. In this line, several studies have tested the efficacy of PAS in recovery functions of the affected upper[29,30] or lower limb[31] by coupling PNS with ipsilesional[29,32] or contralesional M1 stimulation,[33] delivered alone or combined with movement and strength training.[29,33,34] Despite some visible improvements in motor function for some patients, there were no clear changes in motor-related cortical excitability or motor functional responses in the stroke survivors across studies in response to these protocols. It is possible that only stroke survivors who retain some of the spinal cord gating mechanisms and polysynaptic descending pathways from M1 to the peripheral effector may benefit from PAS interventions.[21] Specifically, patients exhibiting greater damage over M1 area are less likely to benefit from PAS protocols potentiating M1-effector pathways. However, they may benefit from PAS protocols targeting descending pathways from compensatory premotor areas instead.

Thus, much like in the way that paired-coil TMS is used to examine functional connectivity between two cortical regions of the stroke-affected network,[29–34] it is indeed possible to apply paired pulses with two TMS coils over two cortical regions in a repetitive manner (Fig. 2). The latter approach is referred to as cortico-cortical PAS (ccPAS),[35,36] and it critically allows to manipulate physiological connectivity in a specific neural route that connect two targeted areas with unprecedented anatomical precision.[37–40] Given that the natural synaptic reorganisation process post-stroke extends across functional networks, ccPAS holds the potential to outperform other forms of NIBS for several key reasons. First, traditional TMS approaches involving single-coil protocols lead to local plastic changes within a cortical area. While such effects may spread to distant, anatomically connected regions, these methods lack the ability to specifically probe synaptic efficacy within preferred anatomical pathways. On the other hand, transcranial electrical stimulation (tES) methods which aim at modulating cortical excitability within a network exert diffuse effects, making the precise manipulation of specific inter-regional pathways challenging. These limitations are critical in stroke rehabilitation, as the functional relevance of specific cortico-cortical connections in motor rehabilitation is highly patient-dependent, varying with the precise location and extent of the lesion. For instance, if a patient exhibits increased activation in the dorsal part of the premotor cortex during action selection, the intervention should strengthen connections between PMd and M1, promoting compensatory mechanisms for M1 damage. By contrast, if greater PMv activation is observed during tasks like object grasping, enhancing connectivity between the ventral part of the premotor cortex and M1 would be more appropriate. ccPAS allows such a level of precision intervention; by increasing or decreasing synaptic efficacy in specific

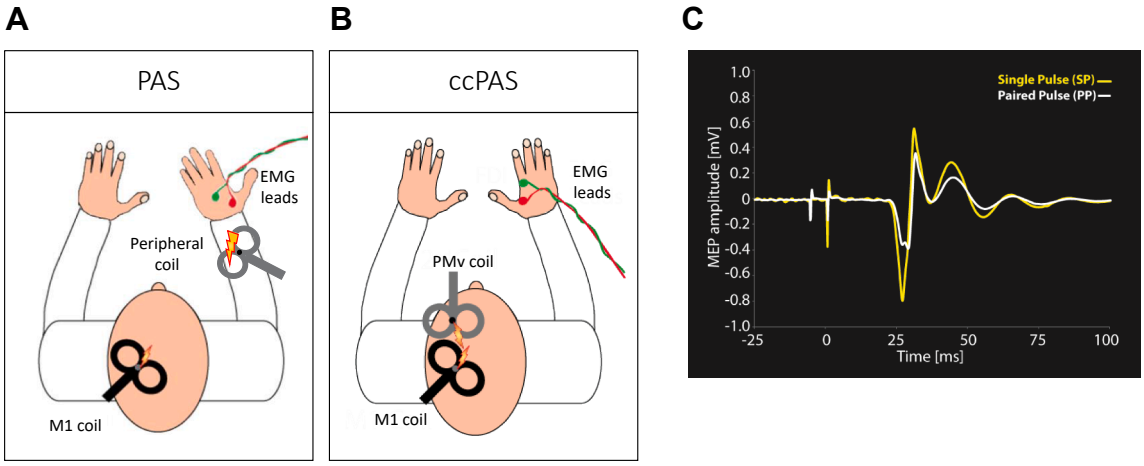

Fig. 2: **A**: PAS protocol involving stimulation on left M1 and on the right median nerve. **B**: ccPAS protocol involving stimulation on left M1 and on the left PMv. **C**: MEP amplitude changes recorded when a single pulse of TMS is delivered on the contralateral M1 (yellow line) and when the single TMS pulse is preceded by a conditioning pulse delivered in the pre-frontal cortex at rest (white line).

cortico-cortical routes connecting distinctive areas of the premotor cortex with M1, ccPAS can differentially promote specific key motor functions. ccPAS can be delivered at rest or during the relearning of motor patterns (motor adaptation), lending itself as a promising neuromodulation approach to tailor interventions that are truly effective for each individual.

Converging evidence from studies with healthy individuals presents ccPAS as a reliable approach to increase synaptic plasticity and connectivity between premotor cortex regions and M1.[36] Most of the ccPAS studies investigating and manipulating connectivity in the motor control network focus on the pathway connecting PMv and M1, showing that increasing PMv-M1 connectivity leads to an increased functional influence of PMv on M1 reflected in enhanced cortical motor responses and motor performance.[37] PMv is connected through direct monosynaptic projections to M1 exerting a powerful influence over M1.[41] Uniquely amongst premotor regions, PMv plays an especially important role in grasping and manipulating objects.[8] A lesion in PMv often results in incorrect finger positioning for grasping and object manipulation, misestimation of grip force, and deficient modulation of M1.[8] Importantly, PMv is critical for post-stroke re-learning of sensorimotor transformations for visually guided actions during upper-limb rehabilitation, where compensatory increase in PMv activity and in the strength of PMv-M1 connections is often observed.[11,12,42] Therefore, we propose that delivering ccPAS over the pathway connecting PMv and M1 to potentiate its synaptic efficacy may improve the relearning of the skills within the injured brain by increasing the functional influence of the healthy PMv through the compensatory mechanism, improving upper-limb function recovery.

Consistent with the bimodal balance-recovery model, this approach is likely to be particularly effective in patients with larger lesions. This notion is supported by a recent study showing that coupling the presentation of a hand-grasping action (which activates the dorsal stream connecting the associative visual cortex to the parietal and premotor cortices) with pulses of TMS over M1 in chronic stroke survivors leads to a muscle-specific increase of cortico-spinal excitability.[43] Such effects are putatively driven by the strengthening of long-range connections between visual and motor control regions promoting visuomotor integration for visually guided actions during recovery. Further evidence of the potential of ccPAS for motor rehabilitation comes from published studies and registered clinical trials where they test ccPAS efficacy in cortico-cortical remapping between different brain areas as shown in Fig. 3.[44–47]

Strengthening connectivity between M1 and areas in the premotor cortex (PMv, PMd), the parietal cortex (posterior parietal cortex) or the visual cortex (associative visual cortex) is crucial for effective upper-limb motor rehabilitation. While the capacity of ccPAS to strengthen such short- or long-range connections and thereby improve the efficacy of learning and adaptation during post-stroke motor rehabilitation is yet to be fully proven, some initial evidence suggests this is indeed possible. For example, Rosso and colleagues (2022)[47] used ccPAS with the aim of increasing synaptic efficacy in the long-range pathways connecting the contralesional cerebellum and the ipsilesional M1. Five sessions of ccPAS in chronic stroke survivors lead to increased blood oxygen level-dependent (BOLD) signal in M1 right after the intervention, followed by an improvement in hand coordination and dexterity after

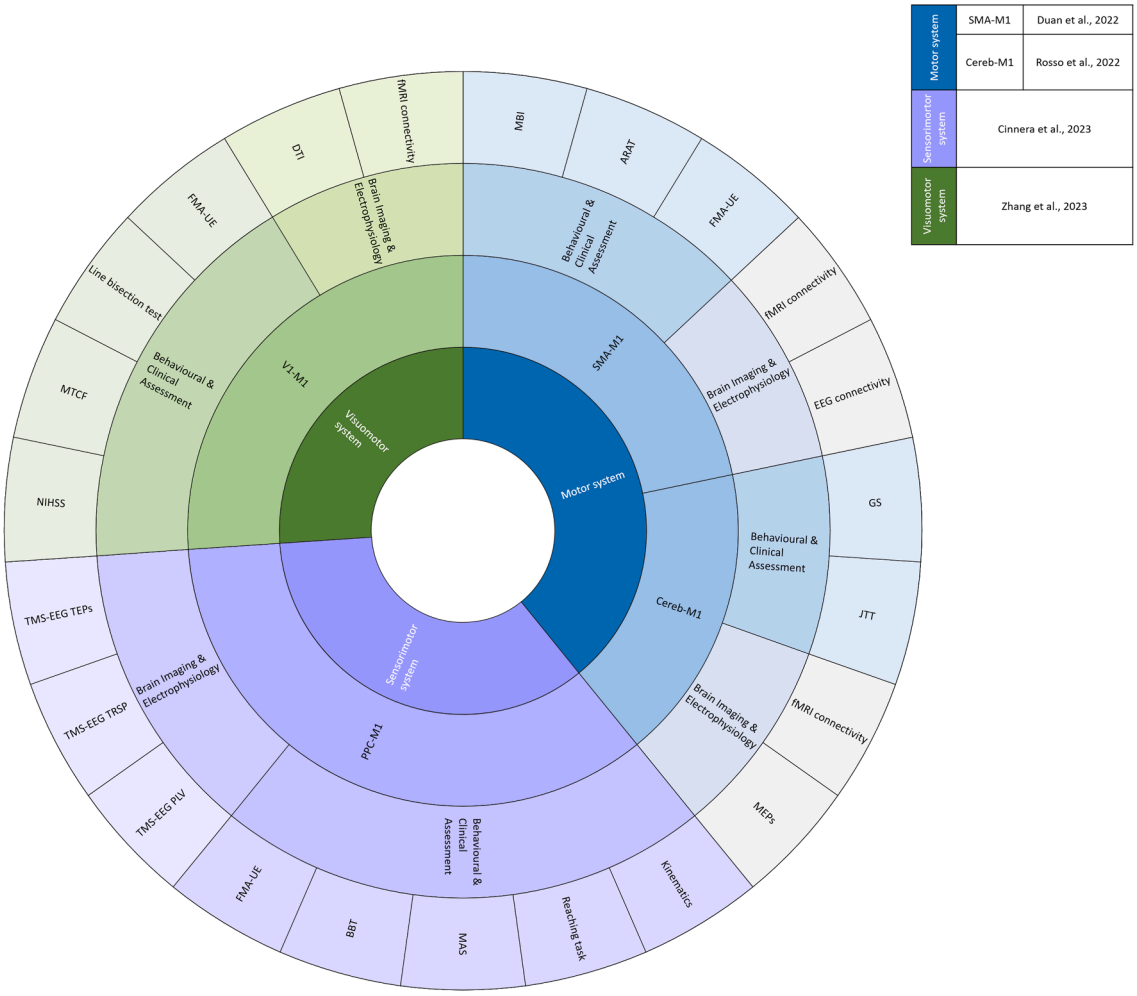

Fig. 3: **Summary of pre-registered clinical trials and a published study (Rosso et al, 2022) using ccPAS for motor stroke recovery.** Abbreviations: SMA = supplementary motor area; M1 = primary motor cortex; Cereb = cerebellum; PPC = posterior-parietal cortex; V1 = primary visual cortex; MBI = Modified Barthel Index; ARAT = Action Research Arm Test; FMA-UE = Fugl-Meyer Assessment of the Upper Extremity; fMRI = functional Magnetic Resonance Imaging; EEG = electroencephalogram; GS = Grip Strength; JTT = Jebsen–Taylor Test; MEPs = Motor Evoked Potentials; MAS = Modified Ashworth Scale; BBT = Box and Block Test; TMS = Transcranial Magnetic Stimulation; PLV = Phase Locking Value; TRSP = TMS-Related Spectral Perturbation; TEPs = TMS-evoked potentials; NIHSS = National Institutes of Health Stroke Scale; MTCF = Modified Taylor Complex Figure; DTI = Diffusion Tensor Imaging.

one month. Notably, not all stroke survivors showed a comparable level of motor improvement. Such inter-individual variability was partially explained by the integrity of the afferent pathway targeted with ccPAS, which highlights the importance of taking the integrity of this pathway into account to tailor interventions.

Another recently published study used ccPAS over the primary visual cortex (V1) and the middle temporal area (MT) to strengthen the connections between these two areas in 16 acute stroke survivors with occipital damaged and homonymous visual field loss. Belvilacqua and colleagues (2025)[48] showed that in increasing the strength of the connections from MT to V1 increased motion direction discrimination. Additionally, those patients with more preserved structural integrity in the ipsilesional pathway connecting V1 with MT also showed enhanced electrophysiological (EEG) coupling between these two regions, as well as EEG coupling with other visual regions. These results showcase the potential of ccPAS to strengthen cortico-cortical connections in stroke rehabilitation. However, further research is needed to assess the translational application ccPAS in stroke motor rehabilitation.

Conclusions and future directions

In this viewpoint, we highlight ccPAS potentiality to improve motor rehabilitation after stroke. We highlight

its ability to manipulate lesion-specific network alterations, paving the way for individualised and effective therapeutic strategies. Nonetheless, there is an incipient need to continue investigating the benefits of ccPAS for neuronal recovery after stroke. Such studies should focus on systematically examining the mechanistic understanding of the effects of ccPAS on neuronal functioning, both locally at the target site, and distally, across the interconnected networks. This challenge may be addressed by combining ccPAS with neurophysiological[36,39,40] (e.g., EEG connectivity measures) and neuroimaging[38,49] (e.g., magnetic resonance spectroscopy) techniques which can offer a deeper understanding of the real effects of NIBS on neuronal networks affected by stroke.

Furthermore, a systematic testing of ccPAS stimulation parameters is essential to clarify mechanisms and dose-effect relationships. Similarlty to recent work in healthy young adults,[36] systematic testing of crucial parameters like inter-pulse interval, pulse frequency, and coil direction (e.g., antero-posterior for precision movements) is essential. Other influential factors include lesion characteristics (duration, size/location), stimulation session number and duration, and neurophysiological and clinical outcome measures. Moreover, scientific rigour, robust methodological designs, sufficient statistical power, and transparent reporting are vital to advance our understanding of ccPAS benefits in stroke recovery. Identifying optimal stimulation parameters will facilitate the development of individualised ccPAS protocols, maximising clinical outcomes for each patient.

Finally, the risks of adverse effects merits attention. Thus far, two patients noted minor, transient issues (headaches, reflex syncope) post-PAS.[47] A systematic investigation of ccPAS risks for stroke survivors across numerous studies is vital to promote its rehabilitation use.

Contributors

Manuscript conceptualisation, literature search, figures and writing were led and coordinated by DF and AS. All authors contributed to the development and refinement of the manuscript and endorsed the decision to submit it for publication.

Declaration of interests

All authors declare no competing interests.

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