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Review

# Paired associative stimulations: Novel tools for interacting with sensory and motor cortical plasticity

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ABSTRACT

In the early 2000s, a novel non-invasive brain stimulation protocol, the *paired associative stimulation* (PAS), was introduced, allowing to induce and investigate Hebbian associative plasticity within the humans' motor system, with patterns resembling *spike-timing-dependent plasticity* properties found in cellular models. Since this evidence, PAS efficacy has been proved in healthy, and to a lesser extent, in clinical populations. Recently, novel 'modified' protocols targeting sensorimotor and crossmodal networks appeared in the literature.

In the present work, we have reviewed recent advances using these 'modified' PAS protocols targeting sensory and motor cortical networks. To better categorize them, we propose a novel classification according to the nature of the peripheral and cortical stimulations (i.e., *within-system*, *cross-systems*, and *cortico-cortical* PAS). For each protocol of the categories mentioned above, we describe and discuss their main features, how they have been used to study and promote brain plasticity, and their advantages and disadvantages.

Overall, current evidence suggests that these novel non-invasive brain stimulation protocols represent very promising tools to study the plastic properties of humans' sensorimotor and crossmodal networks, both in the healthy and in the damaged central nervous system.

## 1. Introduction

Twenty years ago, the research group of Stefan et al. introduced a novel non-invasive brain stimulation protocol, the *paired associative stimulation* (PAS). PAS consists of the repeated, time-locked pairing of two stimulations: a peripheral (i.e., an electric stimulus on the median nerve – MN) and a cortical one, the last represented by a transcranial magnetic stimulation (TMS) pulse over the primary motor cortex (M1). These paired stimuli result in the induction of Hebbian associative plasticity; namely, long-term potentiation (LTP)-like and/or long-term depression (LTD)-like plasticity resembling the timing properties of *spike-timing-dependent plasticity* (STDP) found in cellular models [1]. Since this first study, PAS effects on M1 have been widely replicated and then novel protocols have been developed to test PAS efficacy inside and outside the motor system. At variance with other non-invasive brain stimulation protocols, for which an extensive scientific literature exists, less attention has been devoted to PAS, despite its potentiality for the investigation and modulation of neuroplasticity in primary sensorimotor systems and complex cortical networks, also thanks to the newly developed PAS protocols that interact with local cortical activity and long-range connectivity.

The present review focuses on the more recent PAS paradigms aimed at inducing plastic effects in primary sensory and motor areas. After a brief description of the neurophysiological bases of Hebbian associative plasticity, we will summarize principal findings obtained with the standard PAS protocol combining electric nerve stimulation with TMS pulses over M1 (M1-PAS), considering that this stimulation protocol has been extensively revised elsewhere [e.g., 2–5].

In the core sections of our review, we will provide a state-of-the-art on recent adaptations of PAS that target Hebbian associative plasticity in sensory and motor cortical areas by pairing: *(a)* cortical and sensory stimuli pertaining to the same cerebral system (*within-system* PAS) ; (*b*) cortical and sensory stimuli from different cerebral systems (*cross-systems* PAS), such as an afferent sensory stimulus with motor cortex stimulation; *(c)* two cortical stimulations over different cerebral areas (*cortico-cortical* PAS) (Fig. 1). In each section, we will first describe studies on healthy participants and then, eventually, evidence on the clinical population. Finally, we will discuss theoretical, methodological,

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and clinical implications that arise from these novel brain stimulation protocols.

It has to be noted that PAS protocols targeting frontal cognitive systems, instead of sensorimotor ones, have been recently developed [6–12]; however, they will not be discussed here being out of the aim of the present work and already reviewed elsewhere [13].

## 2. The 'classical' PAS: peripheral nerve stimulation paired with TMS over M1

Since the first theorization in '*The organization of behavior*' (1949), Hebbian associative plasticity has proved to be a fundamental form of plasticity in the nervous system of living beings. As Hebb himself stated: '*the general idea is an old one: that any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated' so that activity in one facilitates activity in the other*' [14]. Hebbian associative plasticity claims that (*a*) temporal and (*b*) causal contingency between the response of two neurons (or two neural systems) leads, over time, to LTP and/or LTD of their synaptic efficacy [15–17]. In the second half of the twentieth century, animal studies and computational models confirmed Hebb's rules, hence the properties of synaptic plasticity [e.g., 18–23]. However, it would be only in the 90s, thanks to the introduction of *in vitro* paired patch-clamp recordings from monosynaptic connections between pyramidal neurons in the neocortex [24], that the importance of temporal contingency between neurons firing could be finally demonstrated as a key factor for the successful induction of Hebbian associative plasticity. In a homosynaptic circuit, LTP can be induced when the pre-synaptic neuron is repeatedly activated *before* the post-synaptic one, while LTD can be induced when the order of the events is reversed (i.e., the pre-synaptic neuron is repeatedly activated *after* the post-synaptic one) and the temporal window between the two stimulations has to be in the order of few milliseconds to successfully induce plastic modifications [25,26]. The timing dependency of neurons firing, responsible for the induction and the direction of plasticity, was translated in the concept of STDP which encloses Hebb's classic theorization on synaptic learning and it is nowadays considered one of the main form of plasticity acting in mammalians' central nervous system [for reviews on STDP neurophysiological substrates, see: 16,27,28].

The first *in vivo* demonstration that a form of associative, timing-dependent, plasticity also applies to human cortical systems was achieved at the very beginning of the twenty-first century thanks to the introduction of the PAS protocol [1]. In their pioneering work, Stefan et al. found that the repeated, time-locked, pairing of electric stimulations of the right MN with TMS pulses over left M1 (i.e., 90 paired stimuli at 0.05 Hz for a total duration of 30 min) led to an increase of motor-evoked potentials (MEPs) amplitude after the end of the stimulation protocol, an evidence of LTP-like plasticity induction in M1. The two paired stimulations converge and interact in the motor system: the MN stimulation indirectly through afferent somatosensory projections to M1 and the TMS directly through the exogenous activation of M1 neurons. Crucially, associative plasticity could be induced only when the inter-stimulus interval (ISI) between the two paired stimulations matched the average conduction time of the corticospinal tract (i.e., about 25 ms). Besides temporal contingency, Stefan et al. identified three other properties considered as key markers of Hebbian associative plasticity: (*a*) topographic specificity (no excitability changes in muscles not innervated by MN), (*b*) persistency (corticospinal facilitation lasting 30−60 min after the end of PAS) and (*c*) reversibility (return to baseline after 60 min).

Subsequently, Wolters et al. found that when the ISI tested in PAS

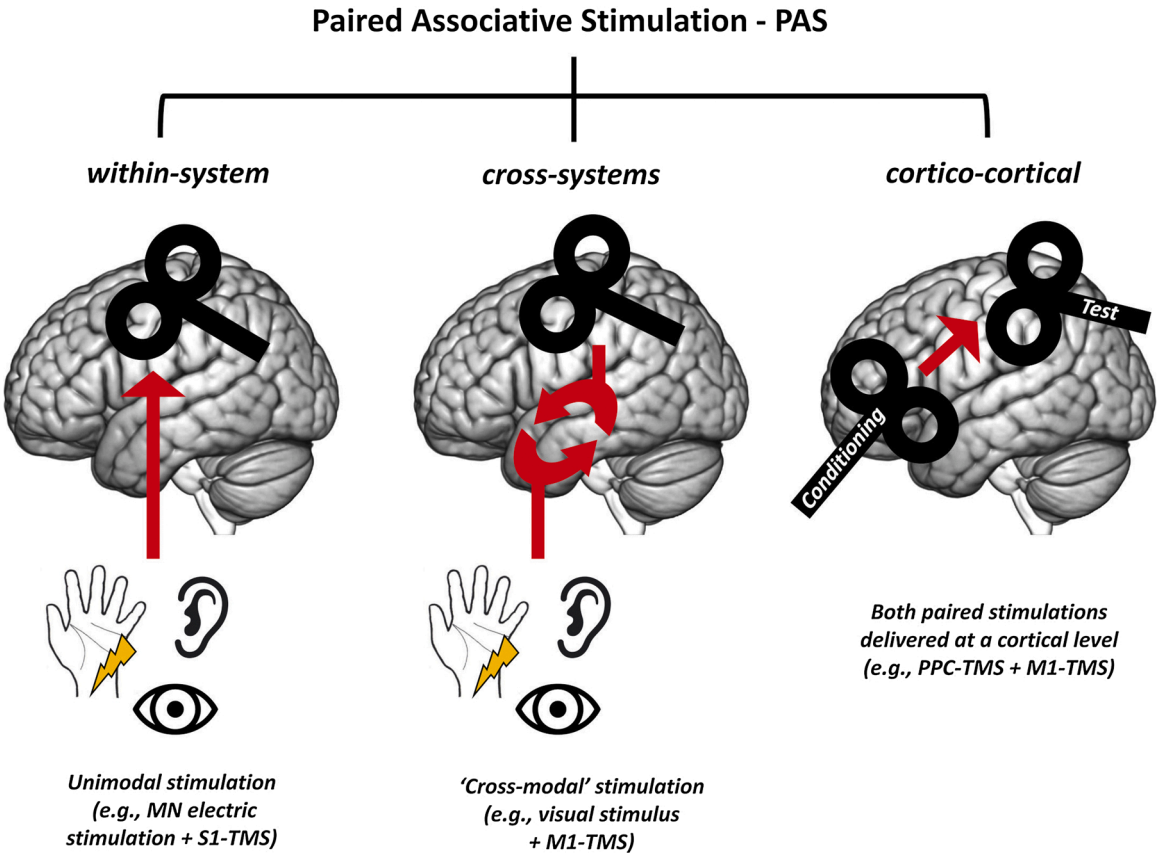


**Fig. 1.** PAS protocols targeting sensory and motor areas can be divided into *within-system*, *cross-systems,* and *cortico-cortical*, according to the characteristics of the paired stimulations and the cortical areas/systems activated. Arrows represent the relationship between the two paired stimulations and are depicted only for visualization purposes. With this classification, the standard M1-PAS should be considered a *cross-systems* PAS (see main text for further information).

**Table 1**
Principal *within-system* PAS protocols targeting motor and sensory systems. Effective protocols or replicated parameters are reported. For the ISIs, we reported all tested ones with such a protocol. ↑ = excitatory effects, ↓ = inhibitory effects, ∅ = ineffective ISI.

| *within-system* PAS | PAS parameters | Peripheral stimulation | Cortical stimulation | ISI | Effects |
|---|---|---|---|---|---|
| **somatosensory system** | | | | | |
| S1-PAS | 180 stimuli @ 0.1 Hz (30 min) | MN-electric stimulation | S1 | SEP N20 + 0 / −2.5 ms<br>SEP N20−20 ms<br>SEP N20−40 / −30 / −10 / −5 / +5 / +10 / +20 / +100 ms | ↑<br>↓<br>∅ |
| | 600 stimuli @ 5 Hz (2 min) | MN-electric stimulation | S1 | SEP N20−2.5 ms<br>SEP N20 + 0 / +2.5 ms | ↑<br>∅ |
| **auditory system** | | | | | |
| auditory PAS | 200 stimuli @ 0.1 Hz (33 min) | 4 Hz tone | Auditory cortex | 10 / 45 ms | ↓ |
| **visual system** | | | | | |
| visual PAS | 90 stimuli @ 0.2 Hz (7 min) | visual pattern-reversal stimulus | V1 | VEP P1 + 25 ms<br>VEP P1−25 ms<br>VEP P1−50 / +50 ms | ↑<br>↓<br>∅ |
| **motor system** | | | | | |
| movement-related PAS | 240 stimuli @ 0.2 Hz (20 min) | voluntary abduction movement | M1 | mean RT (in a thumb abduction task) − 50 ms / − 45 ms<br>mean RT + 100 ms<br>mean RT −100 / +50 / +150 ms | ↑<br>↓<br>∅ |
| motor imagery PAS | 165 stimuli @ ≈0.1 Hz (40 min) | passive opening of the hand (driven by motor imagery) | M1 | 0 ms<br>80 ms | ↑<br>∅ |

was reduced (10 ms), so that the TMS activation of M1 preceded the activation of the same by MN stimulation, PAS after-effects on MEPs amplitude were reversed, leading to a decrease of corticospinal excitability. Thus, not only timing-dependent LTP but also timing-dependent LTD can be induced by the M1-PAS, evidencing that these protocols can be successfully used to study *in vivo* STDP in the human brain [29].

Pharmacological studies showed that PAS-induced plasticity shares important features with LTP/LTD cellular models, such as the mediation of *N*-methyl-D-aspartate (NMDA) receptors and voltage-dependent $Ca^{2+}$ channels [30,31]. Indeed, the use of drugs that are antagonists of NMDA receptors blocks the induction of LTP/LTD plasticity [29,32], while the use of voltage-gated $Ca^{2+}$ channels antagonists, not only blocks the induction of plasticity but reverses its direction [33].

Among the different versions of M1-PAS, worth mentioning are the 'rapid-rate' protocols, with high frequency between the two paired stimulations (usually 5 Hz) allowing to administer hundreds of paired stimuli in a very short time period (e.g., 600 stimuli in 2 min), at variance with the standard versions of the protocol [e.g., 34,35]. Other modified M1-PAS protocols target the lower limbs by delivering the peripheral electric stimulation at the level of a leg's nerve, like the peroneal one, while TMS is administered over M1 leg's area, exploiting ISIs resembling the conduction time of the targeted corticospinal pathway [e.g. 36–38]. In later years also a 'spinal' version of the M1-PAS has been introduced, in which the ISI exploited between the electric nerve stimulation and M1-TMS matches, at a spinal cord level, the orthodromic volleys induced by the cortical stimulation and the antidromic ones induced by the peripheral electric stimulus, hence inducing associative plasticity in the corticomotoneuronal synapses of the corticospinal tract rather than in M1 [e.g., 39–41].

The growing evidence of the efficacy of M1-PAS on healthy individuals [for a review, see: 3,5] led to the application of the protocol in different clinical populations. For instance, M1-PAS has been applied in stroke survivors [e.g., 42–49]. Overall, M1-PAS seems to be effective in enhancing corticospinal excitability of the injured motor cortex when the excitatory protocol (ISI of 25 ms) is applied in chronic stroke patients [42,43,46]. Palmer et al. found a correlation between PAS-induced corticospinal excitability enhancement and enhanced motor performance of the paretic upper-limb [47]. However, other studies in stroke patients that applied the same protocol, or its inhibitory version (ISI of 10 ms), did not found evidence of clinical efficacy of PAS for post-stroke motor rehabilitation [44,45,48,50,51].

Controversial findings of the clinical efficacy of the M1-PAS [for a review, see:, 2] have been also found concerning Parkinson's disease [e.g., 52–57], focal hand dystonia [e.g., 33,57–62], spinal cord injury [e.g., 63–65], Huntington's disease [66] or Giles de la Tourette syndrome [e.g., 67,68]. M1-PAS has also been applied in different neuropsychiatric conditions, like schizophrenia, major depressive disorder, or Alzheimer's disease to study the link between abnormal cortical plasticity, learning and memory deficits [e.g., 69–74].

Overall, further research is needed to better understand the clinical potential of the M1-PAS: the main weakness of this protocol seems to be the high inter-individual variability of neurophysiological effects which mines its potential use as a therapeutic tool [70,75–77].

## 3. *Within-system* PAS protocols

With the term *within-system* PAS, we define those protocols combing peripheral stimulations and TMS pulses processed by the same cortical system. The first modified version of PAS combined somatosensory stimuli with the cortical activation of the primary somatosensory cortex (S1); more recently, *within-system* PAS have been extended for auditory and visual systems. Concerning M1, different movement-related 'peripheral' stimuli were used (Table 1, Fig. 2).

### 3.1. Somatosensory PAS

The somatosensory PAS (S1-PAS) consists in the repeated pairing of a MN electric stimulation with a TMS pulse over the contralateral S1, the last delivered at the latency of the first cortical MN somatosensory-evoked potentials (SEPs) component (i.e., N20), occurring about 20 ms after the MN stimulation onset [78]. In a standard, excitatory, protocol, the stimulation lasts 30 min and comprises 180 paired stimuli delivered at 0.1 Hz. In the pioneering study of Wolters et al., S1-PAS successfully enhanced the P25 component (the second cortical component of SEPs) for at least 30 min, suggesting the induction of LTP. Conversely, when the two paired stimulations were delivered synchronously (ISI of 0 ms) P25 decreased, proving evidence of LTD induction [79]. The after-effects of S1-PAS were further investigated by Litvak

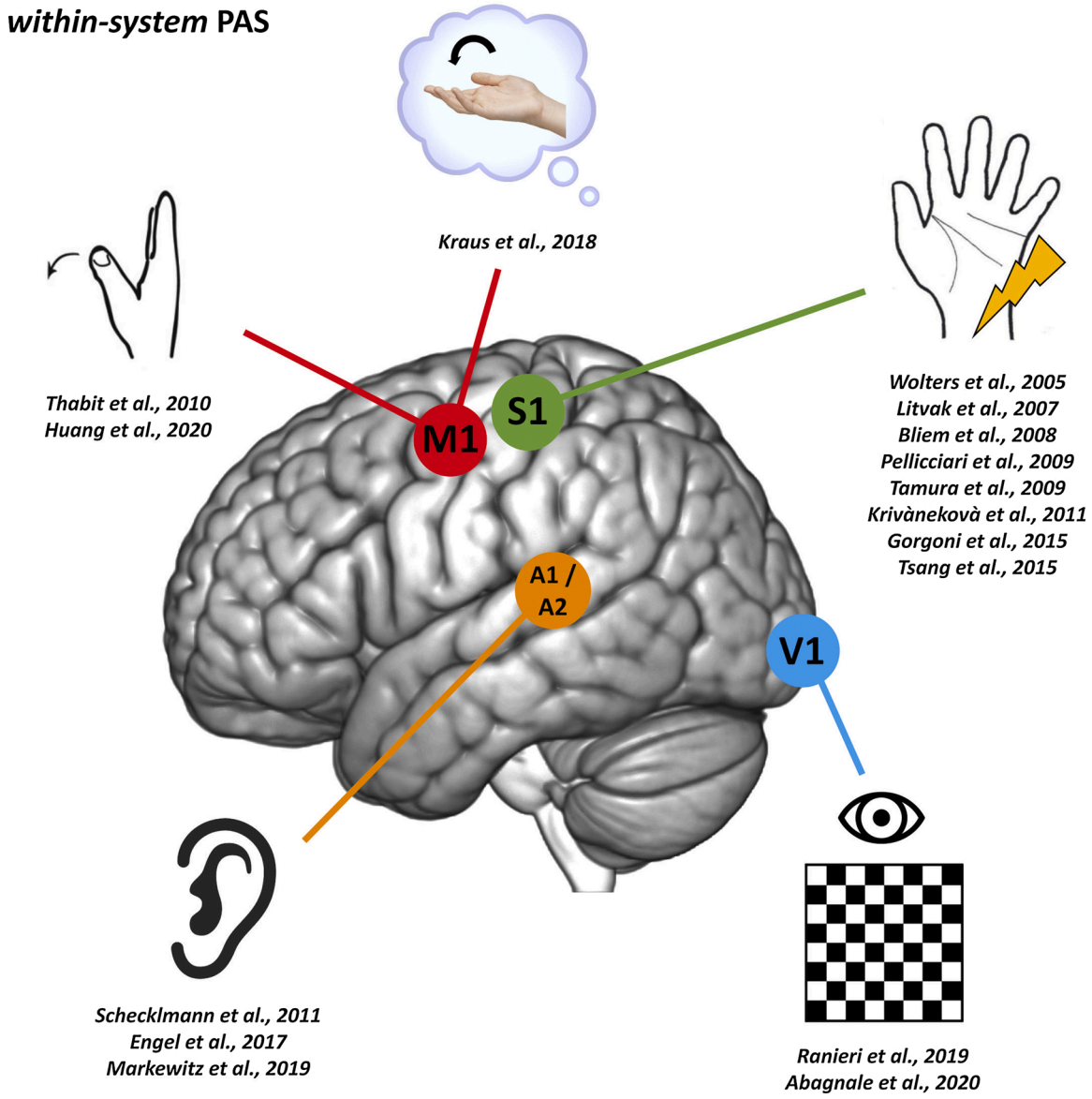


**Fig. 2.** *Within-system* PAS. Colored circles indicate the site of the cortical stimulation (i.e., TMS) associated with the sensory, peripheral, one. The left hemisphere is depicted only for visualization purposes and does not reflect the hemisphere stimulated in the single study or by the single protocol.

et al. [80], who showed that S1-PAS with an ISI of about 20 ms (individual SEP N20 latency *minus* 2.5 ms) decreased tactile acuity in the contralateral (to stimulation) index finger while increased it in the little finger. With an ISI of 0 ms, although effective in increasing tactile acuity in the index finger, no electrophysiological enhancement was detected. Moreover, the authors showed a change of SEPs' topographical maps, specifically at the level of a tangential source located in Broadman area 3b, suggesting plastic effects taking place in the upper layer of S1 [80]. Further investigations revealed that the neurophysiological effects of somatosensory PAS are modulated by age and gender, being larger in elderly (individuals aged > 60 years) and in females [81], while other studies found effects only at an individual, but not at a group, level [82, 83].

The somatosensory PAS was also used to study homeostatic metaplasticity. In a study by Bliem et al., it was found that the S1-PAS alone did not affect somatosensory cortical excitability or tactile discrimination. However, the direction of effects induced by subsequent 20-Hz trains of electrical stimulation of the right MN varied with the preconditioning PAS protocol (i.e., excitatory or inhibitory), suggesting an interaction between the two stimulations [84].

Tsang et al. developed a rapid-rate (5 Hz) version of the S1-PAS [85], which delivers hundreds of paired stimuli in a very short time (e.g., 600 stimuli in 2 min). The rapid-rate S1-PAS increased S1 excitability with a trend for enhancement of SEP N20 and P25 components when the ISI was about 20 ms, similar to the standard S1-PAS. An increase of MEPs amplitude and a decrease of short-latency afferent inhibition was also found, reflecting the spreading of the induced plasticity in M1. Interestingly, the effects on motor cortex excitability were higher than those induced by the 'standard' rapid-rate PAS applying TMS pulses over M1 with an ISI of 25 ms [34], suggesting that the rapid-rate *within-system* S1-PAS may be more effective for acting on sensorimotor plasticity than the motor counterpart. However, no study has yet compared the rapid-rate S1-PAS to the standard S1-PAS [85].

There is only one study exploring S1-PAS effects in clinical conditions [86], namely, in idiopathic focal hand dystonia, a motor disease characterized by uncontrolled, repetitive muscle activity. Abnormal sensorimotor plasticity seems to play a key role in the pathophysiology of focal hand dystonia [e.g., 87–89]; hence, Tamura et al. applied the S1-PAS to further investigate the role of S1 in plastic reorganization in such a disease. They showed an enhancement of SEPs component P25

and an increase of S1 intracortical inhibition in these patients, as compared to healthy individuals, who in this study did not show any response to the S1-PAS [86].

### 3.2. Auditory PAS

A PAS targeting the auditory system was developed by Schecklmann et al. in 2011. The auditory PAS consists of the repeated pairing of an acoustic tone (duration: 400 ms, frequency: 4 kHz, intensity: 60 dB) in the right ear with a TMS pulse over the left auditory cortex. The protocol lasts about 33 min and delivers a total of 200 stimuli at 0.1 Hz. The first study tested two different ISIs (10 ms and 45 ms), based on the assumption that P1, the first cortical component of the long latency acoustic-evoked potentials (LLAEPs) peaked after 50 ms from the onset of the acoustic stimulus. Thus, such ISI should induce associative LTD because the exogenous activation of the auditory cortex by TMS preceded its activation by the acoustic stimulus. Accordingly, the two versions of auditory PAS reduced the N1-P2 complex after their administration, with a greater effect size with the longer ISI. Furthermore, the reduction was present even if the acoustic stimulus had not the same frequency (i.e., 1 kHz) as the one presented during the protocol, suggesting that auditory PAS effects are not tonotopically-specific [90].

In a subsequent study, the influence of tone duration was explored [91]. Engel et al. showed that the auditory PAS with 45 ms of ISI and tone duration of 400 ms, but not of 23 ms, reduced auditory steady-state response, a type of acoustic-evoked potentials used to assess hearing sensitivity [92]. Interestingly, this reduced response was found only when the auditory steady-state response was recorded using a 20 Hz tone, suggesting that the auditory PAS affects plasticity at the level of the secondary auditory cortex [91]. More recently, Markewitz et al. found that the auditory PAS paired with 23 ms tones increased the amplitude of the N1-P2 complex of LLAEPs, conversely to the one using 400 ms tones which decreased it. However, a control protocol with tones lasting 400 ms and sham TMS led to the same reduction of LLAEPs N1-P2 complex observed in the auditory PAS using tones with the same length and real TMS, suggesting that inhibitory effects of such protocols reflect unspecific habituation to the acoustic stimulation [93].

### 3.3. Visual PAS

Ranieri et al. developed a visual version of PAS pairing a visual pattern-reversal stimulus (a black and white checkboard) with a TMS pulse over V1 delivered at 0.2 Hz for a total of 90 trials. The timing dependency of the protocol was tested exploiting different ISIs, accordingly to the individual peak latency of the P1 component of visual-evoked potentials (VEPs), which peaks up, on average, after 100–120 ms from visual stimulus onset and reflects the first activation of extrastriate visual areas [94,95]. When V1-TMS pulses were delivered 25 ms after individual P1 latency, VEPs amplitude and habituation were reduced up to 10 min from the end of the protocol. Conversely, in the PAS where TMS was delivered 25 ms before individual P1 latency, VEPs habituation was enhanced but no effects on VEPs amplitude were recorded. Visual PAS with shorter/longer ISIs (i.e., individual P1 latency *plus* or *minus* 50 ms) were ineffective. The effects on visual processing remain to be assessed [96].

The visual PAS was also used in patients with migraine with aura between attacks [97]: both the protocols (i.e., ISI corresponding to the individual VEPs P1 *plus* 25 ms and *minus* 25 ms) found effective in the healthy participants did not modulate VEPs amplitude and habituation in this clinical population, suggesting that dysrhythmic thalamocortical activity related to migraine may impair bidirectional synaptic plasticity induced by the visual PAS.

### 3.4. Motor PAS

To date, there are also a couple of *within-system* versions of M1-PAS. One of them, which can be considered entirely motor, was developed by Thabit et al. and named 'movement-related cortical stimulation'. This PAS protocol consists of the repeated coupling of a TMS pulse over left M1 and a right-hand thumb abduction movement made by the participant, for a total of 240 stimuli delivered at 0.2 Hz. Firstly, participants were trained on a visuo-motor task which required a button-press with the right thumb every time a visual cue appeared: the participants' mean reaction time at such task was used to set the critical ISI of the PAS protocol. Results showed that when the TMS pulse over M1 was delivered 50 ms before the individual time of voluntary thumb abduction movement, this movement-related PAS enhanced MEPs amplitude; conversely, if TMS over M1 was delivered 100 ms after the onset of the voluntary movement, MEPs amplitude was reduced. These STDP-like effects lasted for 20 min after the end of the protocol and they were found only in the muscle involved in the produced movement (i.e., *abductor pollicis brevis*). Importantly, they were also paralleled by behavioral changes: motor responses with the right hand at a simple reaction time task were shortened after the PAS protocol in which the M1-TMS pulse was delivered before the voluntary movement [98]. A 'hybrid' version of the movement-related PAS was recently tested by Huang et al.. Here, the participant's movement was associated with the standard M1-PAS: an auditory signal warned the participants to make the voluntary movement and, about 45 ms after its onset, the MN electric stimulus paired with M1-TMS pulse was delivered (90 trials at 0.05 Hz; duration: 30 min). Results showed that plastic effects induced by this movement-related PAS were strictly associated with participants' reaction times in making the voluntary movement from the onset of the auditory signal (i.e., faster reaction times, greater MEP enhancement and reduction of short-interval intracortical inhibition), suggesting that multiple convergent sensory inputs can induce long-term plasticity-like effects if the spike-timing-dependent principle for each sensory input is fit [99].

Another *within-system* PAS targeting M1 takes advantage of brain-computer interface. Kraus et al. created a PAS protocol that paired the imagination-driven passive opening of participants' left hand, achieved using a robotic orthosis, and a TMS pulse over the right M1 [100]. The protocol consists of 15 blocks of 11 paired stimulations, for a total duration of 40 min. In particular, during the PAS, participants had to perform a motor imagination task (imagine to open the hand when a visual cue appeared) and sensorimotor event-related desynchronization in the EEG beta-band was used as a marker of motor imagination [101], based on which the TMS pulse was administered. Results showed that when the passive hand movement and the cortical stimulation were synchronous (ISI of 0 ms), there was a significant increase of corticospinal excitability and additional recruitment of corticospinal neurons (i.e., enhanced MEPs amplitude and area). Conversely, the asynchronous PAS protocol (ISI of 80 ms) did not affect corticospinal excitability. Importantly, if the same pattern of paired stimulations was delivered without the concurrent motor imagination task, no effects emerged, proving that this kind of PAS relies on imagery-induced M1 activation rather than the sensorimotor feedback from the passive hand movement [100].

## 4. *Cross-systems* PAS protocols

*Cross-systems* PAS refers to those protocols where the two paired stimulations belong to different sensory systems. Among the *cross-systems* protocols, a further subdivision can be made: *(a) sensory-motor* PAS, where a sensory stimulus is paired with motor cortex activation, and *(b) crossmodal* PAS, where the peripheral stimulus is still a sensory one, but the cortical pulse is not delivered over the motor cortex (Table 2, Fig. 3). Worth mentioning that the original M1-PAS reviewed in the introduction represents a *sensory-motor cross-systems* protocol since it pairs a sensory stimulation (i.e., electric stimulation of a nerve) with the cortical activation of M1.

**Table 2**
Principal *cross-systems* PAS protocols targeting motor and sensory systems. Effective protocols or replicated parameters are reported. For the ISIs, we reported all tested ones with such a protocol. ↑= excitatory effects, ↓ = inhibitory effects, ∅ = ineffective ISI.

| cross-systems PAS | PAS parameters | Peripheral stimulation | Cortical stimulation | ISI tested | Effects |
|---|---|---|---|---|---|
| **sensory-motor PAS** | | | | | |
| auditorymotor PAS | 200 stimuli @ 0.2 Hz (17 min) | speech sound | M1 | 100 ms | ↑ |
| | 600 stimuli @ 5 Hz (2 min) | electric stimulation of the ear nerve | M1 | LLAEP N1 + 50 ms | ↑ |
| visuomotor PAS | 600 stimuli @ 1 Hz (10 min) | visual pattern-reversal stimulus | M1 | VEP P1 + 100 / + 120 ms | ↑ |
| | | | | VEP P1 + 40 ms | ↓ |
| | | | | VEP P1 + 60 / +80 / +140 ms | ∅ |
| mirror PAS | 180 stimuli @ 0.2 Hz (15 min) | visual hand movement | M1 | 25 ms | ↑ |
| | | | | 250 ms | ∅ |
| laser PAS | 90 stimuli @ 0.1 Hz (15 min) | laser stimulation | M1 | N1 LEP + 50 ms | ↑ |
| | | | | N1 LEP + 0 / +100 / +200 ms | ∅ |
| pain PAS | 90 stimuli @ 0.1 Hz (15 min) | electric-nociceptive stimulation | M1 | PREP N2−40 ms | ↓ |
| | | | | PREP N2 + 10 / +30 / +50 ms | ∅ |
| **cross-modal PAS** | | | | | |
| visuo-tactile PAS | 150 stimuli @ 0.1 Hz (25 min) | visual touch stimulus | S1 | 20 / 150 (jittered frequency) ms | ↑ |
| | | | | 20 (jittered frequency) / 60 / 100 ms | ∅ |

### 4.1. Sensory-motor PAS

#### 4.1.1. Auditory-motor PAS

The auditory-motor PAS was developed to access the cortical motor system through audition: indeed, auditory inputs can influence motor activation [e.g., 102,103] given the existence of neural pathways connecting the auditory temporal areas with the precentral gyrus [e.g., 104–106]. The first version of the auditory-motor PAS was introduced by Sowman et al. by pairing an auditory stimulus, hearing the word 'Hey' (intensity: 80 dB) and a TMS pulse over the right M1 with an ISI of 100 ms; this ISI was based on a pilot study showing that MEP enhancement occurs 100 ms after the onset of the auditory stimulus. A total of 200 stimuli were delivered at 0.2 Hz (total duration: 17 min). This auditory-motor PAS increased corticospinal excitability up to 15 min [107].

A similar sensorimotor protocol was tested by Naro et al. in patients with disorders of consciousness (DoC). According to the severity of DoC (unresponsive wakefulness syndrome *vs.* minimally consciousness state), patients may show residual preservation of auditory processing, relying on higher-order associative areas [108,109]. Hence, the authors examined whether plastic effects induced by an auditory-motor PAS protocol might be different according to the severity of DoC. In this study, the auditory-motor PAS paired transauricular repetitive electric stimulations of the right ear nerve with TMS pulses over left M1, delivered at 0.5 Hz in 3 blocks of 200 paired stimuli, with the ISI corresponding to the individual N1 latency of LLAEPs *plus* 50 ms. After PAS, DoC patients with minimally conscious state showed an increase of MEPs amplitude and potentiation of auditory-motor integration markers (i.e., conditioned MEPs after the presentation of a sine tone burst). Conversely, patients with unresponsive wakefulness syndrome did not show any improvement or modification following PAS, probably due to severe auditory-motor connectivity impairment. A group of healthy controls was also tested, showing the same pattern of results of DoC patients with minimally consciousness state [110].

#### 4.1.2. Visuo-motor PAS

In humans, visual information accesses frontal areas through the superior longitudinal fasciculus, a key cortico-cortical white matter pathway that connects occipital areas with premotor ones and is involved in numerous visuo-motor integration processes [e.g., 111,112]. Following this pathway, the visual information takes about 100−150 ms from the first elaboration in V1 to reach the motor system [113,114]. A visuo-motor version of PAS was developed to assess the plastic properties of early-stage visuo-motor integration processes [115]. In the visuo-motor PAS, a pattern-reversal visual stimulus, lateralized to the right visual hemifield, is paired with a TMS pulse over the contralateral M1. A total of 600 stimuli is presented at 1 Hz (duration: 10 min). Suppa et al. tested different ISIs, chosen following individual P1 latency [95]. With an ISI reflecting individual P1 latency *plus* 100 ms, which resembled the conduction time of the superior longitudinal fasciculus, the visuo-motor PAS increased MEPs amplitude, while a shorter ISI, corresponding to P1 latency *plus* 40 ms, inhibited corticospinal excitability. A similar pattern of results was obtained when the protocol was delivered with the same number of trials but with a longer inter-stimuli frequency (i.e., 0.25 Hz between paired stimuli), while the reduction of trials to 150 was unsuccessful. This evidence indicates that visuo-motor PAS effects are dose-dependent but not frequency-dependent, as documented also for classic M1-PAS [1]. Finally, Suppa et al. found that this protocol not only induces local effects in M1 but also modulates functional connectivity between M1 and pre-motor areas. Indeed, premotor-to-motor connectivity, assessed using paired-pulse TMS, increased after the excitatory protocol (ISI corresponding to P1 latency *plus* 100 ms) [115]. The same research group [116] applied the visuo-motor PAS in patients suffering from intermittent photic stimulation-induced photo paroxysmal response (PPR), a condition that is usually associated with epileptic syndromes and abnormal visuo-motor integration [117]. The effect of the excitatory visuo-motor PAS was explored in a group of PPR-positive epileptic and non-epileptic patients, in a group of PPR-negative epileptic patients, and in healthy individuals. The protocol increased MEPs amplitude in all groups, with larger effects in PPR-positive patients, suggesting a correlation between PPR and abnormal plasticity. In a series of subsequent experiments, the inhibitory version of the visuo-motor PAS (individual P1 latency *plus* 40 ms) and a version with an ISI matching P1 latency *plus* 140 ms were compared. The inhibitory protocol reduced MEPs amplitude in PPR positive patients as well as in healthy individuals and, selectively in PPR-positive patients, the protocol with the ISI corresponding to P1 latency *plus* 140 ms was able to induce LTP-like plasticity, mirroring the facilitatory effects obtained with the shorter ISI, hence suggesting a wider temporal window for the induction of plasticity in these patients. Moreover, premotor-to-motor connectivity (as assessed with paired-pulse TMS) decreased, rather than increasing, in PPR-positive patients after the administration of excitatory visuo-motor PAS, suggesting possible structural anomalies in patients' superior longitudinal fasciculus. Clinical outcomes of the different PAS versions were not assessed. Overall, these results support the view that abnormal visuo-motor integration plays a central role in the pathophysiology of PPR but also provide the first evidence that the visuo-motor PAS might be useful to modulate dysfunctional visuo-motor plasticity [116].

Recently, Wolfe et al. investigate the possible effects of administering the visuo-motor PAS in combination with a motor training requiring reaching movements toward visual cues [118]. This protocol increased MEPs' amplitude induced by paired TMS pulses over the superior parietal occipital cortex (*conditioning pulse*) and M1 (*test pulse*) with respect

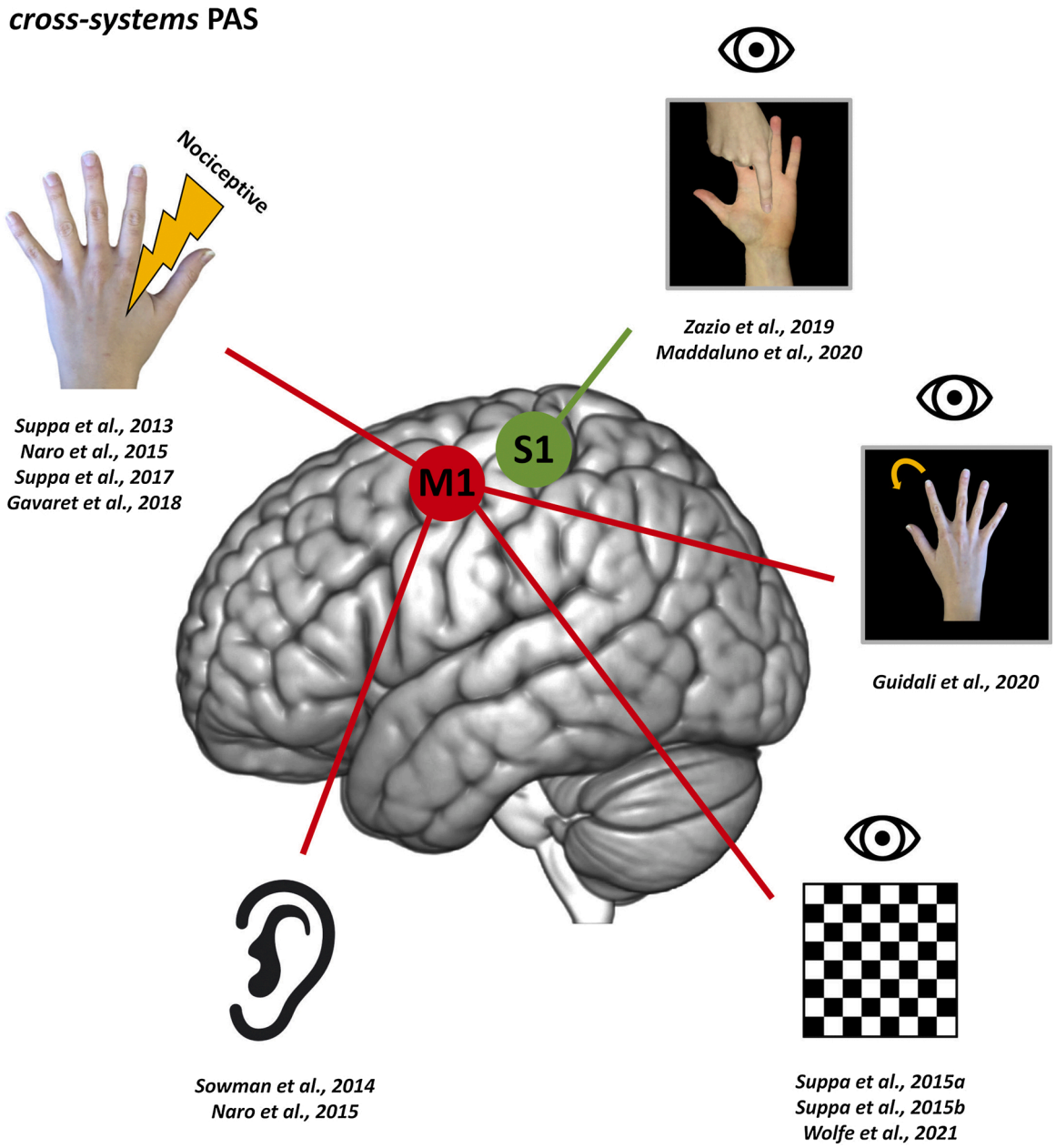


**Fig. 3.** *Cross-systems* PAS. Colored circles indicate the site of the cortical stimulation (i.e., TMS) associated with the peripheral one. The left hemisphere is depicted only for visualization purposes and does not reflect the hemisphere stimulated in the single study or by the single protocol.

to standard single-pulse MEPs. However, similar effects were found also when the visuo-motor PAS was delivered at rest (without motor training), suggesting that concurrent motor learning may not increase the plastic effect of the visuo-motor PAS, at variance with the benefit induced by combining motor practice with repetitive TMS [119].

Another visuo-motor *cross-systems* PAS (mirror PAS) has been developed to investigate the chance of modulating visuo-motor associations in the human mirror motor system, rather than to modulate M1 activity [120]. In the mirror PAS, a TMS pulse over right M1 is paired with a visual stimulus depicting a movement made with the hand ipsilateral to the stimulated hemisphere (i.e., right-hand index finger abduction movement). The protocol consists of 180 paired stimulation delivered over 15 min at a frequency of 0.2 Hz. Since motor resonance (i.e., enhancement of M1 excitability by action observation; [121]) follows somatotopic and mototopic rules, the mirror PAS was used to create a novel visuo-motor association, indexed by an atypical motor resonance effects for ipsilateral hand movements [e.g., 122]. Guidali et al. found that mirror PAS successfully induced an atypical motor resonance effect after its administration, as indexed by the emergence of mirror facilitation of corticospinal excitability during the observation of the ipsilateral hand movement 'conditioned' during the protocol. This effect occurred only when the ISI matched the timing of motor control (25 ms), but not if the visual hand movement was presented 250 ms before the TMS pulse (namely, the possible timing of M1 recruitment following action observation; [123]). Furthermore, the effect of the protocol was specific for the muscle involved in the observed action and not detected when the visual stimulus depicted a non-biological movement [120].

#### 4.1.3. Pain-motor PAS

*Cross-systems* PAS has also been developed to modulate pain processing. Indeed, the motor system plays a crucial role in pain perception and pain modulation [e.g., 124–127], exerting inhibitory control over the areas of the so-called 'pain matrix' [128,129].

Suppa et al. paired painful laser stimulations of the right hand with

TMS pulses over the contralateral (left) M1 (laser PAS). The protocol comprises 90 stimuli delivered at 0.1 Hz for a total duration of 15 min [130]. The ISI was based on evidence that corticospinal excitability is modulated by M1-TMS delivered 50 ms after the N1 component of laser-evoked potential (LEP), which peaks, on average, 160 ms from laser stimulation onset [125]. This protocol enhanced corticospinal excitability only in the muscle receiving the laser stimulation up to 50 min. Importantly, the facilitatory effect was abolished by drug antagonists for NMDA-receptors.

The laser PAS was also applied in clinical settings. In a first study [131], the protocol (with an ISI corresponding to individual LEP N1 *plus* 50 ms) was used in DoC patients with unresponsive wakefulness syndrome, characterized by the absence of motor response to painful stimulations [132]. At a group level, the laser PAS was ineffective on M1 excitability, pain-motor integration markers, and pain perception. However, at a single-subject level, some patients showed a transient enhancement of M1 excitability along with a short-lasting reshaping of pain-motor integration at neurophysiological and clinical levels. This evidence suggests that laser PAS can be used to assess the residual cortical pain processing in DoC. A second study applied laser PAS in Parkinson's disease, investigating whether the presence of chronic pain may influence the protocol efficacy [133]. All patients, independently from the presence of chronic pain or from being on drug treatment, showed reduced MEPs after laser PAS compared to healthy individuals. Then, the laser PAS was compared to the classical excitatory M1-PAS (ISI of 25 ms): patients with Parkinson's disease without chronic pain had similar, reduced neurophysiological responses to both PAS protocols, while in patients with chronic pain only M1-PAS was effective in modulating corticospinal excitability. The conclusion drawn was that chronic pain might influence the response to laser PAS when there is a condition of abnormal pain-motor integration [133].

Finally, there is another pain-motor PAS, named the pain PAS, which combines a nociceptive electric stimulation of the right hand with a TMS pulse over the left M1 [134]. If delivered for 15 min at a frequency of 0.1 Hz (for a total of 90 stimuli), this protocol can decrease MEPs amplitude only if the ISI reflects the individual N2 latency of pain-related evoked potentials [135] *minus* 40 ms. No excitatory effects were reported with longer ISIs. Unfortunately, the nociceptive electric stimulation, even if prevents the risks of skin habituation, at variance with painful laser stimulation, activates a larger number of sensory afferent fibers (A-delta nerve fibers and large-diameter A-beta axons), making it difficult to disentangle the contribution of a specific cortical pathway (i.e., pain-motor *vs.* somatosensory-motor) to pain PAS efficacy [134].

### 4.2. Crossmodal PAS

#### 4.2.1. Visuo-tactile PAS

A crossmodal, visuo-tactile PAS was recently developed [136]. The rationale of this *cross-systems* PAS is based on the existence of visual, mirror-like, responses to touch observation in S1 [137,138]; hence, it pairs a visual stimulus depicting a touch to a left hand with a TMS pulse over right S1, for a total of 150 stimulations delivered at 0.1 Hz (duration: 25 min). The visuo-tactile PAS enhanced 2-point tactile discrimination in the left hand when the ISI was 20 ms, along with an enhancement of the P40 component of SEPs, a late component associated with a first cognitive elaboration of the somatosensory stimulus in S1 [78,139]. With longer ISIs (i.e., 60 or 100 ms), or when the visual stimulus showed a mere hand action, no modulations emerged [136]. The exact neurofunctional mechanism responsible for the effectiveness of 20 ms ISI is still under investigation but likely involves an anticipatory – predictive-like – activation of S1, as suggested by the fact that a longer ISI (150 ms) turned to be effective if paired stimulations frequencies jittered, rather than be fixed [140].

## 5. *Cortico-cortical* PAS protocols

*Cortico-cortical* PAS (cc-PAS) are modified PAS protocols where both paired stimulations are delivered at a cortical level, allowing to directly activate the cortico-cortical pathway connecting two areas. Cc-PAS can be considered both *within-system* and *cross-systems* protocols, according to the stimulated areas. They are very useful protocols to adopt when the connectivity between two cerebral areas (or systems) is well-known, as they allow to causally investigate the plastic properties of these connections and their effectiveness. Then, it should not be surprising that cc-PAS protocols were mainly developed to study connectivity of motor networks (*motor* cc-PAS), even if, recently, a sort of *within-system* cc-PAS has been developed for the visual system (*sensory* cc-PAS) (Table 3, Fig. 4).

### 5.1. Motor cc-PAS

#### 5.1.1. M1-M1 PAS

The first version of the cc-PAS aimed to investigate the plastic mechanisms regulating the interhemispheric M1 connectivity [141]. The M1-M1 PAS pairs TMS pulses over left M1 (*first pulse*) with ones over the homologous area of the right hemisphere (*second pulse*) and thus it can be considered a *within-system* protocol. A total of 90 paired stimulations is delivered at a frequency of 0.05 Hz. The ISI of 8 ms follows the timing of interhemispheric inhibition (IHI) [e.g., 142]. This protocol attenuated left-to-right IHI for at least 60 min while increased MEPs amplitude from the stimulation of right M1. Short-interval intracortical inhibition (SICI) and facilitation (ICF) did not change. By reversing the direction of the paired stimulations (*first pulse* over right M1 and *second pulse* over left M1), right-to-left IHI was still attenuated but left M1 excitability did not change; this last finding was related to manual dexterity. Importantly, the protocol was ineffective in the case of callosal agenesis, suggesting that associative plasticity primarily relies on transcallosal circuits rather than on local M1 stimulation [143]. At the behavioral level, the M1-M1 PAS fastened repetitive finger opposition movements and increased the duration of thumb-index contact, with effects limited to the conditioned hand (i.e., right hand for left-to-right M1-M1 PAS; left hand for right-to-left M1-M1 PAS) and to easy motor sequences of the task, suggesting that the protocol effects did not spread out of M1 [144].

By using a slightly different version of the protocol with an ISI of 15 ms and a frequency between the paired stimulations of 0.1 Hz, Koganemaru et al. found improvements in finger dexterity along with enhanced corticospinal excitability both when the *second* TMS pulse was delivered over the right or the left M1, at variance with the previous findings (see above [145]).

#### 5.1.2. PM-M1 & SMA-M1 PAS

Cc-PAS protocols were also developed to target non-homologs areas of the motor system, such as the ventral premotor (PM) cortex and the caudal part of SMA, which are densely connected to M1 [e.g., 146–150].

In the PM-M1 PAS [151], the *first pulse* is delivered over the left ventral PM and the *second pulse* over the ipsilateral M1 with an ISI of 8 ms, which reflects the conduction time between these areas [e.g., 152]. A total of 90 stimuli is administered at a frequency of 0.1 Hz. At rest, PM-M1 stimulation increased the inhibitory influence of PM over M1, while the same protocol enhanced the excitatory drive from PM to M1 during the engagement in a visuo-motor task. This facilitatory influence turned into an inhibitory one when the order of the paired stimulations was reversed (i.e., *first pulse* over M1 and *second pulse* over PM), suggesting that the direction of LTP- or LTD-like plasticity depends on the direction of the paired stimulations. Plasticity evolved rapidly, lasted for at least 1 h, and began to reverse 3 h after intervention. Conditioning pre-SMA, instead of PM, was ineffective [151]. The PM-M1 PAS also has a behavioral outcome, improving finger dexterity [153]. The neurofunctional underpinnings of the protocol include increased functional

**Table 3**
Principal *cortico-cortical* PAS targeting motor and sensory systems. Effective protocols or replicated parameters are reported. For the ISIs, we reported all tested ones with such a protocol. ↑ = excitatory effects, ↓ = inhibitory effects, ∅ = ineffective ISI.

| cortico-cortical PAS | PAS parameters | first pulse | second pulse | ISI | Effects |
|---|---|---|---|---|---|
| **motor cc-PAS** | | | | | |
| M1-M1 PAS | 90 stimuli @ 0.05 Hz (30 min) | Left / Right M1 | Right / Left M1 | 8 ms | ↑ |
| | 180 stimuli @ 0.1 Hz (30 min) | Left / Right M1 | Right / Left M1 | 15 ms | ↑ |
| | | | | −25 / −15 / −5 / +5 / +25 ms | ∅ |
| PM-M1 PAS | 90 stimuli @ 0.1 Hz (15 min) | ventral PM | M1 | 8 ms | ↓ (at rest) / ↑ (during grasping) |
| | | | | −8 ms | ↓ (during grasping) |
| | | | | 40 ms | ↑ |
| | | | | 500 ms | ∅ |
| SMA-M1 PAS | 150 stimuli @ 0.2 Hz (15 min) | SMA-proper | M1 | 6 ms | ↑ |
| | | | | −15 ms | ↓ |
| | | | | −15 / −10 / 3.2 ms | ∅ |
| PPC-M1 PAS | 100 stimuli @ 0.2 Hz (8 min) | PPC | M1 | 5 / 20 ms | ↓ (at rest) / ↑ (anterior-to-posterior TMS-induced current direction or active muscle contraction during cc-PAS) |
| | | | | −5 / −20 ms | ↑ (at rest) / ↓ (anterior-to-posterior TMS-induced current direction or active muscle contraction during cc-PAS) |
| | | | | −50 / +50 ms | ∅ |
| cerebellum-M1 PAS | 180 pulses @ 0.2 Hz (15 min) | PPC | M1 | 8 ms | ↑ |
| | | | | 100 ms | ∅ |
| | 120 stimuli @ 0.25 Hz (8 min) | cerebellum | M1 | 2 ms | ↑ |
| | | | | 6 / 10 ms | ↓ |
| subcortical-M1 PAS | 180 stimuli @ 0.1 Hz (30 min) | subthalamic nucleus | M1 | 3 / 23 ms | ↑ |
| | | | | 167 ms | ∅ |
| **sensory cc-PAS** | | | | | |
| V5-V1 PAS | 90 pulses @ 0.1 Hz (15 min) | V5 | V1 | 20 ms | ↑ |
| | | | | −20 / 0 ms | ∅ |

connectivity between the stimulated areas, as well in dorsolateral circuits, along with decreased connectivity in the dorsal PM cortex [154]. The PM-M1 PAS may also modulate MEPs amplitude with an ISI of 40 ms [155], a timing corresponding to long-latency inhibitory PM-to-M1 interactions [156], suggesting the potential of this cc-PAS for strengthening connectivity within motor networks through the modulation of indirect pathways [155].

The SMA-M1 PAS [157] pairs TMS pulses over SMA with ones over bilateral M1 (double TMS pulses over left and right M1) at a frequency of 0.2 Hz for a total of 150 stimuli. The protocol increased MEPs amplitude if the ISI was 6 ms, in line with the conduction time of the SMA-to-M1 pathway [158]. Conversely, it decreased M1 excitability if the TMS pulse over M1 preceded the one over SMA by 15 ms. If the first TMS pulse was delivered over pre-SMA, which is not connected with M1 [148], no modulation of MEPs emerged. Interestingly, a critical factor for the success of the protocol seemed bilateral M1 priming: this priming might induce metaplasticity in the SMA-M1 network, which would be necessary for the subsequent induction of plasticity during the PAS protocol [157]. This protocol was also used in patients with Gilles de la Tourette syndrome: the plastic effects induced in these patients are comparable to the ones induced in healthy conditions, hence suggesting that the SMA-M1 connectivity may be unaltered in this neuropsychiatric disorder [159].

### *5.1.3. PPC-M1 PAS*

Another brain region that is connected, both directly and indirectly, with M1 is the posterior parietal cortex (PPC) and the first cc-PAS deploying this cortico-cortical pathway was developed by Koch et al. [160]. The PPC-M1 PAS pairs a TMS pulse over the left PPC (*first pulse*) with a TMS pulse over the ipsilateral M1 (*second pulse*). A total of 100 paired stimulations are delivered at a frequency of 0.2 Hz. The protocol inhibited corticospinal excitability when the ISI between conditioning and test stimuli was of 5 or 20 ms; conversely, the protocol enhanced MEPs amplitude when the stimulation of M1 was 5 or 20 ms before that of PPC (ISIs of -5 ms or -20 ms). These effects lasted for at least 20 min after the end of the protocol. The neurophysiological effects resemble the so-called 'anti-Hebbian' STDP: at a cellular level, for synapses more distant from the soma, the timing required for pre-pairing/post-pairing may shift such that the sign of synaptic modification can be opposite to the classic Hebbian STDP models [e.g., 161]. In other words, LTD may be induced when pre-synaptic cells (here in PPC) fire *before* the post-synaptic ones (here in M1) and LTP may be induced when pre-synaptic cells fire *after* post-synaptic ones. By changing coil orientation and delivering anterior-to-posterior current flow or administering the protocol while participants performed an active muscle contraction with the hand contralateral to TMS, PPC-M1 PAS induced classic Hebbian STDP (LTP induction with ISI of 5 ms and LTD induction with ISI of -5 ms). Thus, with PPC-M1 PAS is possible to induce antithetic forms of associative plasticity (Hebbian and anti-Hebbian) with the same temporal dependency, depending on the stimulation of specific neuronal populations and the activity state of the cortex during the protocol [160]. By using EEG-TMS co-registration [162], it was shown that TMS-evoked potentials (TEPs) over PPC were not modulated; conversely, TEPs over M1 decreased. Furthermore, the excitatory protocol increased alpha-band coherence between the two targeted areas, while the inhibitory one increased coherence only in the beta-band. Since these bands reflect the activity of M1 and PPC [163,164], PPC-M1 PAS seemed to increase phase coupling between these two areas and this increased coupling could, in turn, potentiate the efficacy of cortico-cortical communication in the parieto-motor pathway [162].

By using an ISI of 8 ms and increasing the number of paired stimulations, the PPC-M1 PAS enhanced corticospinal excitability with maximum effects 60 min after the end of the protocol [165].

The parieto-motor PAS was also tested in schizophrenic patients to investigate hemispheric connectivity. Ribolsi et al. found that the excitatory PPC-M1 PAS (ISI of -5 ms) targeting the left hemisphere was ineffective in modulating M1 excitability in schizophrenia, but turned to be effective when it was delivered over the right hemisphere, increasing

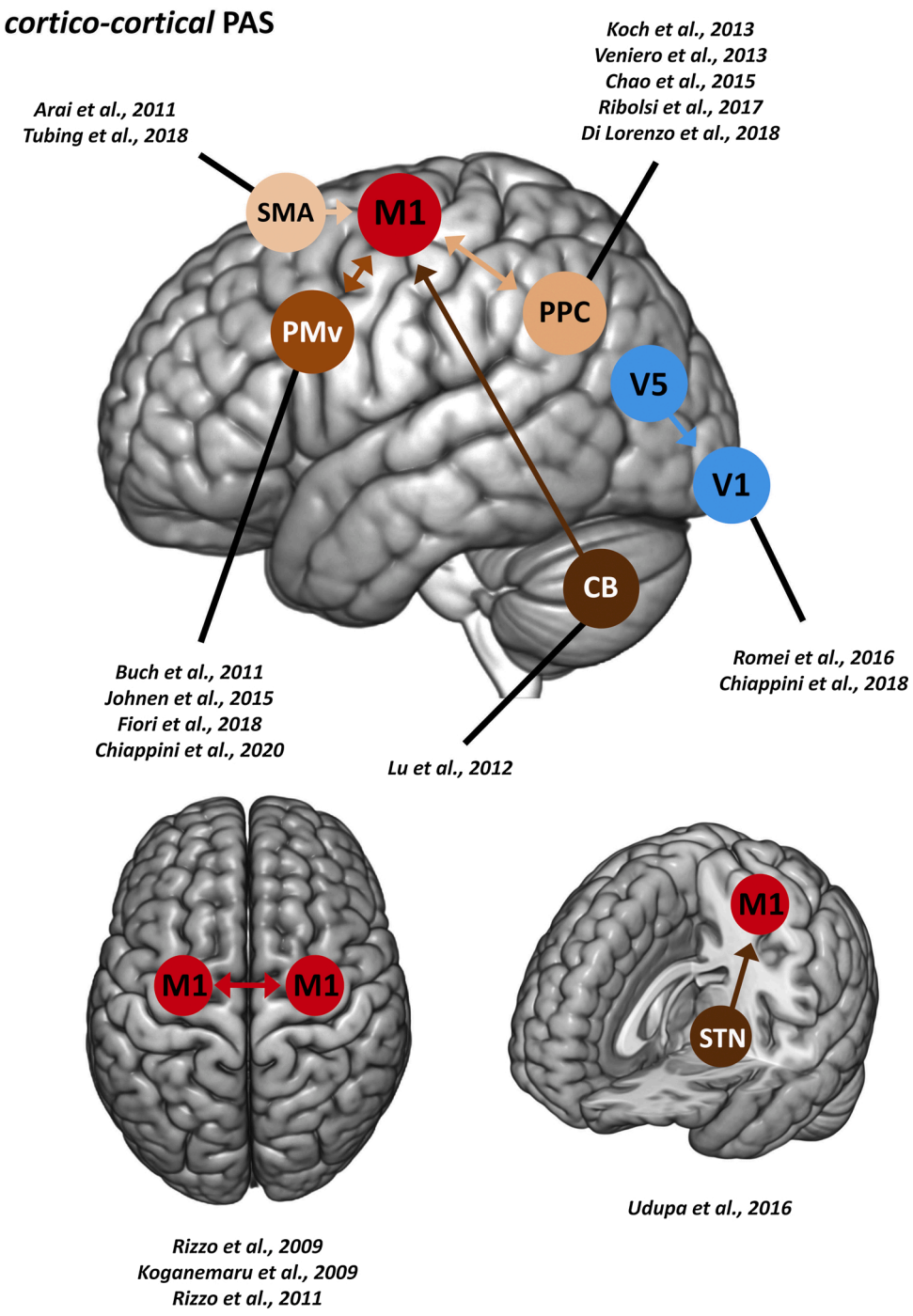


**Fig. 4.** *Cortico-cortical* PAS. Colored circles indicate sites of cortical stimulations; arrows indicate the direction of the cortico-cortical connection tested. The left hemisphere is depicted only for visualization purposes and does not reflect the hemisphere stimulated in the single study or by the single protocol.

corticospinal excitability 20 min after the end of the protocol. Noteworthy, in healthy participants, the PPC-M1 PAS induced comparable excitatory effects in both hemispheres [166]. The effects of PPC-M1 PAS were also explored in Alzheimer's disease: both LTP-inducing (ISI of -5 ms) and LTD-inducing (ISI of 5 ms) protocols were ineffective at least in modulating corticospinal excitability, providing support to the hypothesis of impaired cortico-cortical STDP in this form of dementia [167].

#### *5.1.4. Cerebellum-M1 & subcortical-M1 PAS*

To target long-range M1 connectivity, two PAS protocols were developed: one targeting the cerebellar-dentato-thalamo-M1 pathway [168], the other exploiting the stimulation of a basal ganglia-cortical pathway [169].

The cerebellum-M1 PAS repeatedly pairs TMS pulses over the right cerebellum with ones over the left M1. A total of 120 stimuli are delivered at a frequency of 0.25 Hz for a protocol length of 8 min. This cc-PAS was effective in decreasing MEPs amplitude when the ISI was of 6 or 10 ms (i.e., the time of cerebellar-motor inhibition; [170]); conversely, with an ISI of 2 ms, MEPs amplitude increased. Cerebellar-motor inhibition, as assessed with paired-pulse TMS, was not modulated by the protocol, suggesting that this kind of PAS affected associative plasticity within M1 rather than in the cerebellar-cortical pathway [168].

The subcortical-M1 PAS developed by Udupa et al. was used to

investigate abnormal connectivity between the basal ganglia and M1 in Parkinson's disease [169]. This protocol pairs deep brain stimulation of the subthalamic nucleus (*first pulse*) with M1-TMS (*second pulse*). Over 30 min, a total of 180 stimuli is delivered at a frequency of 0.1 Hz. As assessed with deep brain stimulation of basal ganglia, the best ISIs to enhance MEPs amplitude is of ~3 ms (short-interval) and ~23 ms (medium-interval) [171]. Accordingly, the same ISIs applied to the subcortical-M1 PAS increased M1 excitability for 45 min after the end of the protocol, with no effect on ICF and SICI. At a longer ISI (i.e., 167 ms), the PAS was ineffective. Clinical effects were not assessed [169].

### 5.2. Sensory cc-PAS

#### 5.2.1. V5-V1 PAS

The only cc-PAS on sensory areas targets the connectivity between the visual motion area (V5) and V1 (V5-V1 PAS) [172]. Back projections from extra-striate areas to V1 subtend visual motion awareness [e.g., 173,174]; for this reason, Romei et al. used the V5-V1 PAS for enhancing visual motion sensitivity. Their protocol pairs TMS pulses over left V5 with ones over V1, exploiting an ISI of 20 ms, consistent with the V5-to-V1 conduction time [175]. A total of 90 paired stimulations are delivered at 0.1 Hz (duration: 15 min). This protocol improved performance at a motion coherence discrimination task, lowering the motion sensitivity threshold. Conversely, no motion sensitivity changes occurred with synchronous paired stimulations (ISI of 0 ms) and when the direction of the stimulation was reversed (*first pulse* over V1 and *second pulse* over V5) [172]. Chiappini et al. applied V5-V1 PAS in a state-dependent manner. To engage direction-specific V5 neurons during the PAS, participants had to observe stimuli moving in a specific direction. Under this condition, the V5-V1 PAS enhanced motion sensitivity selectively when motion direction was congruent to the one used during the protocol. Interestingly, these effects were found only when the *first pulse* intensity was below the phosphene threshold; conversely, when the intensity was set at the phosphene threshold, the function-tuning V5-V1 PAS was ineffective. This evidence indicates that the administration of V5-V1 protocol in a state-dependent manner with the same parameters of the 'at rest' version blocks the induction of plasticity occurring in resting states. Consequently, the activation state of the visual cortex is a key factor for the successful induction of associative plasticity [176].

## 6. General discussion

The various modified PAS protocols represent valuable non-invasive brain stimulation paradigms to study and modulate plasticity in sensory and motor networks. PAS paradigms are obviously very different from the ones used in cellular or *in vitro* models to study and induce LTP/LTD. In this last case, the spatial and temporal features of a synaptic circuit are easier under control and thus, the potential influence of confounding factors can be minimized [31]. In the following paragraphs, we discuss PAS theoretical, methodological, and clinical implications, highlighting commonalities and differences between classes of different protocols, as well as their strengths and weaknesses.

### 6.1. Key elements for PAS efficacy

The fundamental aspect that emerges from the present revision of the PAS literature is that LTP-like and/or LTD-like plasticity can be induced at different levels in sensorimotor systems. Hebbian principles of synaptic plasticity seem to extend beyond the first stage of cortical sensory and motor processing, encompassing sensorimotor and crossmodal networks. The neurophysiological and behavioral changes induced by all the PAS protocols are characterized by timing dependency, input specificity, persistency, and reversibility, suggesting a common neurophysiological substrate at the basis of the plastic effects induced by PAS, despite their methodological differences [2,5,177].

The knowledge of chronometry of sensory and motor processing, as well as structural and functional connectivity within and between cortical networks, represents the basis of every PAS protocol. The circuitries underlying *within-system* PAS, and thus the peripheral-to-cortical pathways exploited by these protocols, had been well explored by neurophysiological studies. This is the case of the somatosensory afference used in S1-PAS and M1-PAS: somatosensory information travels along the spino-thalamo-cortical pathway, taking about 20 ms to reach S1 and 25 ms to M1; in fact, S1-to-M1 sensory transfer takes about 5 ms [1,79,178]. The auditory PAS considers that sounds activate the auditory cortex after about 50 ms [179] and, according to Hebbian plasticity principles, anticipating the activation of the auditory cortex with TMS leads to LTD [90]. In the visual PAS, to induce LTP, the optimal ISI corresponds to the time necessary for the visual information to reach V1 [96]. Similarly, in cc-PAS the timing of cortico-cortical interactions is crucial. The M1-M1 PAS [143,145] relies on the timing of the trans-callosal transfer of information [142,180], as well as other cc-PAS protocols targeting intra-hemispheric short-range [e.g., 150] and long-range [e.g., 181] connectivity within the motor network rely on the timing of the exploited cortico-cortical pathways.

Timing dependency also includes the concept of temporal window put forward in the introduction: the classic STDP asymmetrical window (i.e., LTP and LTD depend on different ISIs) has been found in the majority of the studies using *within-system* PAS and cc-PAS [e.g., 79,96,98,151,157,160,168]. Conversely, only one *cross-systems* PAS [115] succeeded in inducing both LTP and LTD. This evidence allows to speculate that STDP-like mechanisms may be absent, or at least different, in more complex systems of our brain; however, this latter hypothesis is difficult to believe considering that different computational models using STDP showed the effectiveness of this form of plasticity in spiking neural networks [e.g., 182–185]. It is worth noting that in PAS protocols targeting primary systems the conduction time of the stimulated pathways is easier to control. By taking advantage of the EEG literature, the latencies of the first cortical components of sensory-related evoked potentials give reliable clues of the time course through which an afferent sensory stimulus activates its primary sensory cortex, facilitating the choice of the optimal ISI to create a condition of simultaneity (or non-simultaneity) between the two paired stimulations of PAS. This is also true for cc-PAS targeting the motor system, for which paired-pulse TMS literature gives strong hints about the conduction times of the cortico-cortical pathways [e.g., 152,170,175]. Conversely, the choice of ISIs to be used in *cross-systems* PAS protocols is not so straightforward (see next paragraph). In the same vein, for those PAS targeting long-range connectivity, the effective ISIs for driving excitatory/inhibitory changes is difficult to be set *a-priori*. For instance, the PPC-M1 PAS [160] is effective in inducing excitatory effects in M1 both with an ISI of 5 and of 20 ms; similarly, the visuo-motor PAS [115] induces LTP-like effects with an ISI corresponding to the individual P1 latency *plus* 100 ms and *plus* 120 ms.

Other factors that contribute to the effectiveness of PAS, regardless of the specific protocol, are metaplastic and cortical state-dependent phenomena occurring during the protocol administration. Metaplasticity refers to a higher-order form of synaptic plasticity, based on which the activity-dependent synaptic plasticity becomes a dynamic process that changes as a function of the integrated prior activity of the postsynaptic neuron [186]. Using the M1- and S1-PAS, it was highlighted how such protocols could be successfully used to investigate homeostatic and non-homeostatic properties of the motor and somatosensory systems, also showing an influence of S1-PAS on S1 neurons responses to a subsequent peripheral electric stimulation [e.g., 84,187,188]. The plastic effects of the visuo-motor PAS are thought to involve non-homeostatic metaplastic interactions between PAS-induced heterosynaptic visual-to-motor STDP and homosynaptic LTD-like plasticity [115]. Considering cc-PAS, the fact that the SMA-M1 PAS requires priming with near-simultaneous TMS over M1 suggests that this priming induces metaplastic phenomena within M1 mediating the success of the

subsequent PAS protocol [157]. However, habituation to sensory stimulation may mask, or overcome, TMS effects. An example comes from the auditory PAS: the inhibitory effects found in the original work [90] are now considered controversial [93] since that they may be merely caused by the repeated exposure to the peripheral acoustic stimulus.

The cortical-state dependency of PAS effects is also relevant for the effectiveness of the protocol and the direction of the induced plasticity. Brain state-dependency of TMS is a well-known characteristic of this brain stimulation technique [189]; hence, it is not surprising that also PAS protocols share this feature. For example, at the same ISI, the PM-M1 PAS administered at rest induces LTD, while administered during a task induces LTP [151]. Similarly, the V5-V1 PAS delivered during a visual task enhances motion sensitivity according to viewed stimuli, with no effects for unprimed motion direction [176].

Similar to other non-invasive brain stimulation paradigms, individual factors contribute to the effectiveness of the PAS protocols. Indeed, the main feature, and somehow the main limitation, of PAS seems to be the high inter- and intra-individual variability of their effects. For example, if one considers the M1-PAS, it seems that, on average, about 40 % of the tested participants are 'PAS non-responders' and, within the same participant, PAS outcomes are not always stable [e.g., 75–77,190]. To overcome this issue, recent studies have considered the possibility of including only 'PAS responders' (preliminarily identified) into their experimental samples, thus reducing the variability of outcomes [e.g., 74,75,190,191]. Many factors may preclude PAS effects, among which participants' attention during the protocol administration or participants' age and gender [192]. However, further research is needed to draw conclusions and to explore the extent such factors influence the outcomes of modified PAS [e.g., 76,77]. To date, the S1-PAS is the only modified protocol based on a good number of researches. After the first promising results [79–81], more recent investigations suggest a lack of replicability and high inter-individual variability [83,84,86,193]. The variability of S1-PAS results allows us to point out an important methodological issue linked to these studies that may have mined their effectiveness. Indeed, besides individual factors, such as participants' level of attention or arousal during the administration of the protocol [192,194], another possible factor of variability is the use of PAS with slight modifications of the stimulation parameters concerning the original protocols, as shown in S1-PAS studies [83,84,86,193]. Especially for *within-system* PAS targeting peripheral-cortical pathways the use of averaged ISIs (i.e., ISI not based on the individual conduction time, which can be determined, for instance, by recording sensory event-related potentials) may contribute to inter-subject variability, reducing PAS efficacy. All these aspects should be taken into careful consideration in the development of PAS protocols targeting complex or crossmodal cortical systems.

Despite the complexity and methodological differences between different PAS protocols, these plasticity-induction tools provide a new frame to investigate the functional interplay of sensorimotor networks.

In conclusion, the different types of PAS (i.e., *within-system*, *cross-systems,* and cc-PAS) share a lot of functional features, highlighting the usefulness of such protocols to assess and modulate plastic mechanisms and interactions between different cortical regions and across different activation states. At the same time, they also underline the neurophysiological complexity at the basis of these protocols, which has to be taken into account for the effectiveness of such a class of non-invasive brain stimulation techniques.

### 6.2. Cross-systems PAS: a novel frame to study sensorimotor networks in humans

*Cross-systems* PAS, as well as cc-PAS targeting long-range connectivity, carry numerous advantages with respect to *within-system* protocol in the study of sensorimotor networks and their related properties. Thus, we believe that in the future, the number of studies adopting this class of PAS protocols will increase. Long-range connectivity between different brain regions is thought to be indispensable in cortical computations that integrate different types of signals and information processed across multiple cerebral areas [195]. While in animal models these interactions can be easily investigated using invasive methods, in humans, this goal is obviously harder to achieve. *Cross-systems* PAS, by targeting long-range connectivity between different cortical systems, represents a very useful tool to explore the functional properties of such interactions, acting at a higher hierarchical level than *within-system* protocols.

Sensorimotor networks are endorsed with very flexible cortical subcircuits, characterized by rapid adaptation to changes of cognitive and sensory processing demanded on a fast timescale [196]. PAS itself is a very flexible stimulation technique since the combinations of peripheral and cortical stimulations' properties are potentially infinite. The only limitation is that an anatomical or functional pathway has to exist between the two cerebral nodes, acting as neural substrates for the induced plasticity [197]. This evidence opens up to a lot of possible implications of *cross-systems* PAS within the field of sensorimotor processing and/or crossmodal integration.

For example, in the future, more selective *cross-systems* PAS could be developed to stimulate very 'specific' cortical pathways of human's motor systems (e.g., reaching and grasping control systems, peripersonal action fields, ventral *versus* dorsal attentional networks, dorsomedial *versus* dorsolateral sensorimotor streams; see: [198–200]), hence targeting selective components of action control or sensory processing. Moreover, the recent developments in multisensory integration research can foster the exploitation of novel PAS protocols where a sensory stream is used to gain access to a cortical area processing a different sensory modality. Crossmodal interactions are supported by either direct, feed-forward connections between primary sensory areas, as well as by feedback projections from the association of multisensory areas (e.g., posterior parietal and superior temporal cortices) to primary sensory areas [e.g., 201,202]. In this framework, *cross-systems* PAS may allow to assess and modulate these pathways in a timing-dependent way, by varying the order of the paired stimulations and the content of the peripheral stimulus. In this regard, the visuo-tactile PAS [136] can be considered the first step in such a direction; nevertheless, the application of *cross-systems* PAS in the field of crossmodal integration is only at its beginning.

Crucially, the fact that *cross-systems* PAS allows to precisely stimulate only the 'starting' and the 'final' point of a cross-cortical circuit, leaves a potential 'grey' area in the interpretation of the protocol's effects – namely, what happens in between at a synaptic level (and thus which parallel pathways may be responsible for the induction of plasticity) that can only be speculated or explored by adopting concurrent neurophysiological techniques like EEG. As stated above, in *cross-systems* protocols, it cannot be excluded that bidirectional interplays in the communication of two nodes of the PAS-targeted network may influence timing-dependency and effectiveness of the protocol itself. In most *within-system* protocols the peripheral-to-cortical transmission in the stimulated circuit is unidirectional, e.g., relying on thalamocortical feed-forward afferences from the sensory organs. Conversely, in complex brain networks, communication between areas is intrinsically bidirectional [203,204], with feed-forward connections on the one hand, and feed-back influences on the other. For instance, cc-PAS protocols like the PPC-M1 or the PM-M1 offer an interesting benchmark of such evidence in a 'controlled' setting where a cross-cortical pathway can be selectively activated by taking advantage of the focality of the coupled TMS pulses. Indeed, in these protocols, reversing the order of conditioning and test pulses while maintaining the same ISI, induces opposite plastic phenomena or different effects in the targeted area, proving the bidirectionality of the stimulated pathway [151,160].

Another potential issue of PAS protocols targeting complex networks is the possible influence of high-order 'cognitive' factors, which may shape the direction of the plastic modifications or the effectiveness of the ISIs. For instance, the visuo-tactile PAS seems to rely on the activation of anticipatory, predictive-like, mechanisms, which influences PAS by

restricting the ISI for vision-touch interactions [140].

Certainly, the neurophysiological complexity of *cross-systems* PAS can be seen as a drawback for the success of the protocol itself; however, such complexity also represents the main advantage of this class of protocols concerning *within-system* ones. In fact, *cross-systems* protocols can be viewed as the 'evolution' of area-specific PAS: namely, they can be used, not only to induce (and investigate) associative plasticity within the stimulated area/system but, in a broader perspective, also to study its neurophysiological and connectivity properties like the direction and conduction time within the targeted pathway, the contribution of other areas within the targeted network, the chance to influence the response of the targeted area through indirect pathways and so on. Furthermore, acting at a network level (as happens in *cross-systems* PAS) may increase the efficacy and reliability of the PAS effects with respect to *within-system* protocols targeting a single primary area. In fact, different studies show that the development of crossmodal and multisensory integration processes within the mammalian brain is mediated by associative mechanisms [e.g., 205–209] and, thus, in humans, *cross-systems* PAS, by affecting associative learning, might be a very suitable tool to explore and modulate the functional properties of such complex networks. Future studies should directly compare whether the effects induced by *within-system* protocols within a cortical region are similar in magnitude to the ones of the *cross-systems*. For example, by assessing whether the visuo-tactile PAS is more effective in inducing associative plasticity in the somatosensory system than the S1-PAS or differences between the plasticity induced in the visual system by the visual PAS and by its cortico-cortical counterpart (i.e., V5-V1 PAS).

Overall, it is true that the neurophysiological complexity at the basis of *cross-systems* PAS introduces more confounding factors, maybe also increasing the variability of outcomes with respect to *within-system* PAS. However, we also believe that this class of PAS protocols would represent a fertile ground for future research in the field of non-invasive neuromodulation, allowing to better study the neurophysiological substrates of complex sensorimotor interactions and multisensory integration.

### 6.3. Clinical potential of modified PAS

Unfortunately, very few studies have been conducted in clinical populations, and the majority of them focused on the neurophysiological changes induced by PAS in a diagnostic/prognostic perspective, leaving open their therapeutic potential. Some 'proof-of-concept' studies have already highlighted how modified PAS protocols can be used to investigate abnormal associative plasticity in neurodegenerative diseases [133,167,169], focal hand dystonia [86], disorders of consciousness [110,131], schizophrenia [166], migraine [97], or Tourette's syndrome [159], allowing to confirm (or disconfirm) neuropathophysiological models of these clinical conditions.

The modified PAS protocols discussed here may open up new avenues for sensorimotor rehabilitation. Up to now, the classical M1-PAS has been used in post-stroke patients to assess, and more rarely to change, motor system plasticity with controversial and debated results [e.g., 42,43,47–51,210]. However, modified PAS have the advantage of allowing access to the injured system via spared sensorimotor or crossmodal pathways. It has to be considered that intra- and inter-hemispheric changes in sensorimotor coupling constitute an important pathophysiological marker of post-stroke motor and sensory impairments [211] and that clinical recovery does not rely only on the induction of local LTP-like processes, also requiring enhanced network connectivity [212]. Hence, PAS protocols – and especially *cross-systems* ones – could represent a new strategy to reinforce suboptimal sensorimotor interactions by potentiating the transmission of sensory inputs to the motor system via spared pathways. The chance of affecting perilesional plasticity by targeting functionally intact sensory or motor areas could represent a more effective strategy for optimizing network flexibility and improving clinical deficits. On the other hand, different PAS protocols could also be used to examine sensorimotor and crossmodal plasticity with the aim of choosing the optimal therapy on a tailored basis.

Further research is mandatory to verify the effects of different PAS protocols in clinical populations in order to better define the pathophysiology of diseases as well as to probe the plastic reorganization of a dysfunctional system.

## 7. Conclusion

As extensively described in the present review, novel PAS protocols have been developed in the last ten years, showing their usefulness, but also their actual limits, in exploring sensorimotor plasticity in the human brain. Recent evidence also showing the effectiveness of cc-PAS on cognitive functioning [13] provides further support of the goodness and potential of this non-invasive brain stimulation tool for neuroscientists and even for clinicians.

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## CRediT authorship contribution statement

**Giacomo Guidali:** Conceptualization, Methodology, Investigation, Visualization, Writing - original draft. **Camilla Roncoroni:** Methodology, Investigation, Writing - original draft. **Nadia Bolognini:** Conceptualization, Methodology, Supervision, Writing - original draft.

## Declaration of Competing Interest

The authors declare no competing interest.

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