

**Neurophysiological correlates of plasticity induced by *paired associative stimulation* (PAS) targeting the motor cortex:
a TMS-EEG registered report**

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ABSTRACT

Paired associative stimulation (PAS) can induce long-term potentiation (LTP) and long-term depression (LTD) in the human motor system by applying transcranial magnetic stimulation (TMS) pulses on the primary motor cortex (M1) paired with electrical stimulation of the contralateral median nerve. Previous studies have primarily assessed the effectiveness of M1-PAS by measuring corticospinal excitability (i.e., motor-evoked potentials – MEPs) or behavioral outcomes. Concurrent TMS and electroencephalography (TMS-EEG) co-registration can provide further evidence about cortical patterns of M1-PAS-induced plasticity. In the present work, we will take advantage of the TMS-EEG technique to track the cortical dynamics related to M1-PAS, aiming to better characterize the neurophysiological substrates grounding the effectiveness of such protocol, providing evidence about the specificity of early TEPs components in reflecting the M1 functional activity and connectivity changes underpinning PAS effects.

In two counterbalanced, within-subject sessions, healthy participants will undergo the standard M1-PAS protocols inducing LTP (i.e., exploiting an interstimulus interval – ISI – between paired stimuli of 25 ms) and LTD (i.e., exploiting an ISI of 10 ms) while measuring MEPs and M1-TEPs before, immediately after, and 30 minutes from the end of the protocol, both at supra- (i.e., 110%) and sub- (i.e., 90%) resting motor threshold intensities. The spatiotemporal profile of early evoked cortical responses and connectivity patterns will be deeply investigated.

Overall, our study will foster evidence about the use of TMS-EEG biomarkers to track complex plastic changes induced in the human brain by non-invasive brain stimulation protocols based on associative mechanisms, like PAS.

Keywords: transcranial magnetic stimulation (TMS), electroencephalography (EEG), motor cortex, paired associative stimulation (PAS), brain plasticity, TMS-evoked potential

INTRODUCTION

Paired Associative Stimulation is a class of non-invasive brain stimulation (NIBS) protocols that are known to induce long-term potentiation (LTP) and long-term depression (LTD), following Hebbian rules of associative plasticity (Hebb, 1949). In PAS protocols, the induction of plasticity is achieved through the repeated pairing of two different stimulations, which are known to activate the same cortical areas or circuits (for a review, see: Suppa et al., 2017).

The standard version of the PAS targets the motor system. It pairs transcranial magnetic stimulation (TMS) pulses over the primary motor cortex (M1) with the electrical stimulation of the contralateral (to TMS) median nerve (M1-PAS) (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Depending on the inter-stimulus interval (ISI) between these two stimulations, LTP or LTD is induced within the motor system, according to the asymmetric time window of spike-timing-dependent plasticity (STDP) observed in the cellular and animal models (Caporale & Dan, 2008; F. Müller-Dahlhaus, Ziemann, & Classen, 2010). In detail, when the ISI **closely resembles** the timing in which the afferent sensory signal from the median nerve electrical stimulation reaches M1 (i.e., 25 ms), LTP is induced (PAS_{LTP}), with an increase in post-PAS MEPs amplitude (Conde et al., 2012; Fratello et al., 2006; Nitsche et al., 2007; Stefan et al., 2000; Wolters et al., 2003; Ziemann, Ilić, Pauli, Meintzschel, & Ruge, 2004). Conversely, when the ISI is shorter (i.e., 10 ms) and, thus, the exogenous activation of M1 induced by TMS precedes the endogenous one driven by the electrical stimulation, LTD is induced (PAS_{LTD}) (Batsikadze, Paulus, Kuo, & Nitsche, 2013; Delvendahl et al., 2010; Huber et al., 2008; Stefan et al., 2006; Wolters et al., 2003). The effectiveness of this protocol has been widely replicated in the last two decades (**Kumru et al., 2017; J. F. M. Müller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008; Player, Taylor, Alonzo, & Loo, 2012; Quartarone et al., 2006; Schabrun, Weise, Ridding, & Classen, 2013**) (for reviews, see: Suppa et al., 2017; Wischniewski & Schutter, 2016), and modified versions targeting other cortical areas/networks than M1 arose in recent years (**Borgomaneri et al., 2023; Casarotto et al., 2023; Engel, Markewitz, Langguth, & Schecklmann, 2017; Guidali, Bagattini, De Matola, & Brignani, 2023; Guidali, Carneiro, & Bolognini, 2020; Nord et al., 2019; Ranieri et al., 2019; Santarnecchi et al., 2018; Zazio, Guidali, Maddaluno, Miniussi, & Bolognini, 2019; Zibman, Daniel, Alyagon, Etkin, & Zangen, 2019**) (for reviews, see: Guidali, Roncoroni, & Bolognini, 2021b, 2021a). Proving to be effective tools for inducing LTP/LTD effects, PAS protocols have been extensively used in clinical research to investigate abnormal plasticity in

several neuropsychiatric populations (Brandt et al., 2014; Castel-Lacanal, Marque, & Tardy, 2009; Crupi et al., 2008; Frantseva et al., 2008; Kuhn et al., 2016; Tolmacheva et al., 2017).

To date, the majority of the studies has been evaluating the effectiveness of the M1-PAS induced plasticity within the motor system by focusing on corticospinal excitability (i.e., motor-evoked potentials – MEPs) or behavioral measures as primary outcomes (Carson & Kennedy, 2013; Suppa et al., 2017).

In the last two decades, concurrent TMS and electroencephalography registration (TMS-EEG) has been extensively used to assess cortical excitability and connectivity before and after non-invasive brain stimulation, leveraging the sensitivity of TMS-evoked potentials (TEP) to track global changes induced by neuromodulation (for review, see: Cruciani et al., 2023). To the best of our knowledge, up to the present, only two studies (Costanzo et al., 2023; Huber et al., 2008) investigated M1-PAS aftereffects using TMS-EEG.

In a seminal work, Huber and coworkers (2008) measured TMS-evoked activity before and after PAS_{LTP} and PAS_{LTD} to assess modulations of the cortical responses by different ISIs. Results showed that, in single subjects, TMS-evoked cortical responses over sensorimotor cortex changed according to the protocol exploited, representing the first direct evidence that PAS can induce changes in global cortical dynamics. However, in this paper, the authors exploited the global mean field power as the primary variable of interest without analyzing single M1-TEP components profile. Moreover, they qualitatively report differential effects of the two PAS protocols on cortical excitability when applied at different cortical sites, suggesting complex effects of the stimulation protocols on M1 effective connectivity patterns (Huber et al., 2008).

Recently, Costanzo and colleagues (2023) showed that, after the administration of PAS_{LTP}, the amplitude of P30 and P60 components of M1-TEPs increased. Different studies showed that the P30 reflects local circuits' excitatory neurotransmission (Bonato, Miniussi, & Rossini, 2006; Ferreri et al., 2011; Paus, Sipila, & Strafella, 2001). Along the same line, a P60 modulation was associated with TMS protocols known to influence M1 excitability (e.g., Esser et al., 2006; Rogasch, Daskalakis, & Fitzgerald, 2013). No significant correlation was found between increased MEP amplitude and the modulation of single TEP components after the protocol administration. This suggests that peripheral and cortical measures of PAS efficacy frame two different facets of induced plasticity within M1. The study exclusively explored the facilitation effects of PAS (specifically, PAS_{LTP}) and analyzed the aftereffects by looking at amplitude modulations of the M1-TEP components only immediately after the protocol's administration. (Costanzo et al., 2023).

In the present study, exploiting TMS-EEG, we aim to deepen the cortical underpinnings of M1-PAS induced-plasticity. This investigation is crucial to derive the cortical biomarkers of plastic changes in the human brain. To this end, our study aims to characterize better the neurophysiological substrates grounding the effectiveness of non-invasive brain stimulation protocols based on associative mechanisms like PAS ones (e.g., Chung, Rogasch, Hoy, & Fitzgerald, 2015; Ferreri & Rossini, 2013; Kallioniemi & Daskalakis, 2022).

In a within-subjects experiment, healthy participants will undergo PAS_{LTP} and PAS_{LTD} protocols (delivered in two different sessions), investigating the spatiotemporal profile of cortical excitability changes (i.e., M1-TEPs) and connectivity patterns within the motor system before and after the administration of these two M1-PAS protocols. MEPs will be recorded as the control variable; namely, we expect that the two protocols would lead to opposite patterns on corticospinal tract excitability, which could be interpreted as LTP- or LTD-like induction within the motor system (Suppa et al., 2017). These patterns will serve as operative models to discuss the results found on cortico-cortical measures. Indeed, as the *positive control* condition of our study (**H0**), we aim to replicate the corticospinal enhancement and inhibition after PAS_{LTP} and PAS_{LTD}, respectively (Wischniewski & Schutter, 2016). Namely, MEPs recorded after PAS_{LTP} is expected to have a greater peak-to-peak amplitude than the ones recorded in baseline, and the opposite pattern should be observed for PAS_{LTD}. This analysis will confirm that our two PAS protocols will be effectively induced in the expected direction according to previous literature.

Considering PAS effects on early M1-TEP components (i.e., P30 and P60 – **H1**) reflecting local excitability (e.g., Cash et al., 2017; Esser et al., 2006), for the PAS_{LTP} protocol, we expect to replicate the same pattern of modulation found in the study of Costanzo and coworkers (2023), i.e., enhancement of P30 and P60 amplitude after PAS_{LTP} administration. For PAS_{LTD}, if LTD induction led to the modulation of the same TEP components, we speculate that P30 and P60 would show an amplitude reduction. **Crucially, P30 and P60 are often used as biomarkers of cortical excitability in TMS-EEG studies assessing the effects of non-invasive neuromodulation techniques inducing LTD/LTP-like phenomena within the motor system (Cruciani et al., 2023).**

In detail, P30 is thought to reflect fast excitatory mechanisms within the M1 local circuit (Mäki & Ilmoniemi, 2010; Rogasch et al., 2013). Hence, P30 was reported to be positively correlated with MEP amplitude (Ferreri et al., 2011; Mäki & Ilmoniemi, 2010). Corroborating this hypothesis, intermittent (iTBS) and continuous (cTBS) theta-burst TMS – used to transiently increase and suppress motor cortex excitability, respectively –

influence P30 amplitude in the same direction of MEP modulations. For instance, inhibition of P30 was found following cTBS (Vernet et al., 2013) and Gedankien and colleagues (2017) showed that changes in N15-P30 TEP and MEP amplitudes were significantly correlated (Gedankien, Fried, Pascual-Leone, & Shafi, 2017). On the other hand, P60 component has been associated with the activity of recurrent cortico-cortical and cortico-subcortical circuits reflecting glutamatergic signal propagation mediated by AMPA receptor activation (Belardinelli et al., 2021). Previous TMS-EEG evidence showed that the P60 component can be modulated by drugs influencing gamma-aminobutyric acid (GABA) neurotransmission (Gordon, Belardinelli, Stenroos, Ziemann, & Zrenner, 2022), suggesting that P60 amplitude likely reflects an excitation/inhibition balance of the stimulated region. In fact, different TMS and transcranial direct current stimulation interventions significantly modulated the amplitude of the TMS-evoked P60 after their application (Chung et al., 2019; Mosayebi-Samani et al., 2023).

Considering later M1-TEP components (**H2**), it is well known that the N100 is a marker of inhibitory processing mediated by GABA receptors and different studies related the modulation of this component to the induction of inhibitory-like phenomena or plastic effects (Bonnard, Spieser, Meziane, De Graaf, & Pailhous, 2009; Casula et al., 2014; Premoli et al., 2018; Premoli, Rivolta, et al., 2014; Rogasch et al., 2013). Similarly, we expect that the N100 is influenced by PAS_{LTD} administration. Hence, considering the inhibitory nature of this component, we hypothesize that PAS_{LTD} administration would lead to a greater (negative) amplitude of this component. Noteworthy, Costanzo et al. (2023) did not find any significant modulation of the N100 after PAS_{LTP}. So, given the controversial literature on N100 modulations after the administration of excitatory TMS protocols (Bai, Zhang, & Fong, 2021; Chung et al., 2019; Desforges et al., 2022; Goldsworthy et al., 2020), PAS_{LTP} effects will be investigated exploratory.

Then, we will deepen the duration of PAS aftereffects on cortical excitability (**H3**). Namely, whether PAS modulations recorded at a cortical level exhibit the same temporal evolution as the effects typically observed on MEPs. To this aim, MEPs and TEPs will also be assessed after 30 minutes from the PAS administration. Previous studies showed that PAS aftereffects are detectable in a time window of about double the time of protocol duration (Suppa et al., 2017; Wischniewski & Schutter, 2016; Wolters et al., 2003). Hence, based on previous evidence and considering that our PAS protocols will last 15 minutes (see **Methods and Materials**), we hypothesize that induced plasticity patterns fade away about 30 minutes after the end of the protocol, likely

for both PAS_{LTP} and PAS_{LTD} . If this is true, we expect a significant difference to emerge when comparing TMS-evoked activity (i.e., P30, P60, N100, and MEP amplitude) after the intervention with the one recorded after 30 minutes.

Finally, different studies argued that the interpretation of the functional meaning of P60 might be possibly hampered by confounding factors related to the elaboration of afferent proprioceptive signals related to MEPs (e.g., Fecchio et al., 2017; Komssi, Kähkönen, & Ilmoniemi, 2004), with respect to early components (i.e., P30, e.g., Petrichella et al., 2017). This aspect complicates the interpretation of P60, making it difficult to disentangle the contribution of peripheral processing to the amplitude increases of this cortical component found after PAS. In detail, as previously noted for the PAS_{LTP} (Costanzo et al., 2023), we hypothesize that, in such protocol, the change in P60 magnitude could be overestimated because of the involvement of MEP refference (**H4**). To rule out this hypothesis and provide more detailed information for the overall interpretation of the results (if a significant modulation of P60 is found in **H1**), before and after PAS administration, M1-TEPs will also be recorded at a subthreshold intensity (i.e., 90% of participant's resting motor threshold – rMT), besides being recorded at a standard suprathreshold intensity (i.e., 110% rMT). If the refferent signals have a major impact on P60 amplitude modulation, we expect that, compared to P30 (which is too early and allegedly unaffected by MEP refference), P60 will display a greater change in amplitude in the suprathreshold condition after PAS_{LTP} administration, due to the MEP presence. Noteworthy, previous literature showed that TEPs could be successfully recorded at subthreshold intensities, displaying the same typical components as suprathreshold TEPs (Komssi et al., 2004; Lioumis, Kičić, Savolainen, Mäkelä, & Kähkönen, 2009).

Overall, our study aims to explore possible cortical markers of Hebbian associative LTP- and LTD-like plasticity in the motor system exploiting the PAS protocol. This investigation will take advantage of concurrent TMS-EEG registration, investigating spatiotemporal and connectivity patterns after the administration of excitatory and inhibitory M1-PAS (see **Table 1** for all our *a priori* hypotheses and related planned analysis).

----- *Insert Table 1 here* -----

MATERIALS AND METHODS

Participants

Healthy participants (age range: 18-40 years) will be recruited for the present study. All participants must be right-handed, as assessed with the Edinburgh handedness questionnaire (Oldfield, 1971), with no contraindications to TMS administration following TMS safety guidelines (Rossi et al., 2021), and no history of neurological, psychiatric, or other relevant medical conditions. Participants taking medications known to affect PAS effects (i.e., corticosteroids, anxiolytics, centrally acting ion channel blockers, or antihistamines) will be excluded from the study, **unless, at the time of the first session of the experiment, they have not taken such medications for at least one month prior to the assessment** (Suppa et al., 2017). Each participant will complete a safety screening questionnaire to exclude the presence of contraindications to TMS (Rossi et al., 2021) and give informed written consent before participating in the study. The study will be performed in the TMS-EEG laboratory of the University of Milano-Bicocca following the Declaration of Helsinki, and it is currently submitted to the local Ethics Committee pending approval. All participants will belong to the same experimental group and undergo the same procedures. Participants will be naïve to the testing procedures and will be debriefed immediately after the end of the last session.

Sample size estimation

Here, we provide the rationale for the sample size estimation of each experimental hypothesis (**Table 1**). All the analyses were conducted using the software G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009), with an alpha of 0.02 and a power of 0.9. Of all of them, we ultimately considered the largest sample size for the present study.

a) *H0 (positive control): Effects of PAS protocols on MEP amplitude*

Considering the available literature on the effects of PAS_{LTP} and PAS_{LTD} on corticospinal excitability, we expect that PAS_{LTP} will induce an increase, as compared to baseline, in peak-to-peak MEP amplitude right after its administration. At the same time, PAS_{LTD} is supposed to reduce MEPs (Suppa et al., 2017; Wischnewski & Schutter, 2016) after its administration. In a meta-analysis by Wischnewski and colleagues (2016), the authors evaluated the effects of PAS_{LTP} across 70 experiments performed in 60 studies and found a significant potentiation of corticospinal output (as indexed by MEPs amplitude) right after PAS_{LTP} administration (Cohen's $d = 1.44$). On the other hand, the analysis

of 39 PAS_{LTD} studies demonstrated a consistent depression of cortical excitability levels compared to baseline immediately after the protocol ($d = 2.04$). We used information from this meta-analysis to retrieve Cohen's d values for the planned t-tests and focused on the smaller effect size between the two (i.e., $d = 1.44$). To account for potential publication bias (Anderson, Kelley, & Maxwell, 2017), we have considered half of the reported Cohen's d value ($d = 0.7$) for power analysis. Hence, the estimated sample for a one-tailed dependent sample t-test resulted in 25 participants.

b) H1: Effects of PAS protocols on early positive TEP components (P30 and P60)

Concerning the effects of PAS on early TEPs (i.e., P30 and P60), we considered the study by Costanzo et al. (2023), which is, to date, the only published report of a TMS-EEG experiment evaluating the effects of a PAS_{LTP} protocol on these specific M1-TEP components. From this article, we considered the reported significant interaction between 'Condition' and 'Time' factors ($F_{3,45} = 8.469$, $p = 0.011$, partial eta-squared – $\eta_p^2 = 0.361$) for our sample size estimation (Costanzo et al., 2023). As for the previous estimation, to account for potential publication bias, we have considered half of the reported η_p^2 (i.e., $\eta_p^2 = 0.18$) for a 2 X 2 rmANOVA power analysis. The estimated sample resulted in 10 participants.

c) H2: Effects of PAS_{LTD} on the N100

Based on previous literature about LTD and M1-TEPs (Casula et al., 2014), we hypothesize an **enhancement (i.e., greater negativity)** of the late N100 TEP component after delivering PAS_{LTD}. In the absence of a similar comparison in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008), **we based our estimation on the work by Casula et al. (2014) which found M1-TEP N100 enhancement after low-frequency (i.e., inhibitory) repetitive TMS. The authors reported a difference in N100 amplitude over fronto-central electrodes of $1.88 \pm 0.66 \mu\text{V}$ corresponding to a Cohen's d of 2.85 (Casula et al., 2014). As for the previous estimations, to account for potential publication bias, we have considered half of the reported d (i.e., $d = 1.42$) for our power analysis. Here, the estimated sample size for a one-tailed dependent sample t-test is 10 participants.**

d) H3: Temporal evolution of induced plasticity

We will evaluate the temporal evolution of the two PAS protocols. We sought to determine whether the effects of the two protocols disappear when evaluated 30 min after the end of stimulation. **Sample**

size estimation is based on the work by Costanzo and colleagues (2023), reporting a significant main effect of ‘Time’ ($F_{2,30} = 4.679$, $p = 0.047$, $\eta_p^2 = 0.238$) after PAS_{LTP} administration and exploiting three timepoints as in our study. As for the previous estimations, to account for potential publication bias, we have considered half of the reported η_p^2 (i.e., $\eta_p^2 = 0.119$) for our rmANOVA power analysis. The estimated sample was found to be 18 participants.

e) H4: Effects of TMS pulse intensity on the modulation of P30 and P60 after PAS_{LTP}

Finally, to rule out the potential contamination of the P60 component by MEP-related afferent signals in the PAS_{LTP}, our study will examine P30 and P60 modulations elicited by both suprathreshold and subthreshold TMS pulses. We chose to focus our hypothesis only on the PAS_{LTP} based on the study of Costanzo et al (2023) which specifically addressed P60 modulation in PAS_{LTP} and noted the possible influence of MEP reafference limiting the interpretation of the results. Given the lack of knowledge about PAS_{LTD}-induced effects, we will not register this hypothesis and the same analysis will be carried out exploratory if **H5** is confirmed. Considering only PAS_{LTP}, in the absence of a comparison between supra- vs. subthreshold TEPs in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008) and previous TMS-EEG literature testing the effects of stimulation intensity in a pre- versus post-intervention experimental design as ours, we run a 2 X 2 rmANOVA power analysis hypothesizing a medium effect size ($\eta_p^2 = 0.06$) (Fritz, Morris, & Richler, 2012). Notably, given the effect sizes found in previous literature that has explored M1-TEP modulations by applying TMS below or above the individual rMT (Lioumis et al., 2009), as well as in trials with or without MEPs (Petrichella et al., 2017), this value is configured as sufficient to detect statistically significant effects of interest. Here, the estimated sample size is 29 participants.

Taken together all the sample size estimations for our hypotheses, 30 participants will be recruited for the study to allow proper counterbalancing of the experimental conditions. If needed, to make up for the possibility of dropouts or outliers (see **Exclusion criteria**), additional participants will be recruited until the required 30 complete datasets are reached.

Exclusion criteria

Participants will be excluded from the study if one of the following criteria is met:

- a) Participants failed the initial screening – i.e., they resulted left-handed on the Edinburgh questionnaire (EHI score below 0), presented contraindications to TMS according to Rossi et al.'s safety guidelines, or made chronic/acute use of PAS-influencing medications as reported in the **Participants** section.
- b) Participants did not complete all the experimental procedures or both sessions.
- c) TMS intensity exceeds 80% of the Maximum Stimulator Output (MSO) in at least one session.
- d) MEP amplitude, TEP P30, P60, and N100 amplitude exceeding 3 SD from the group mean in at least one recording block.
- e) More than 10% of the EEG channels are marked as bad (i.e., broken, excessive noise) by visual inspection of the trials during TMS-EEG preprocessing in at least one of the recording blocks.
- f) Less than 20 TMS-EMG trials or 100 TMS-EEG trials survive after trial rejection during preprocessing in at least one of the recording blocks.
- g) TMS-EEG cleaned data have low signal-to-noise ratio – SNR (< 1.5) defined as the ratio of mean absolute amplitude of EEG during the 300 ms post-TMS period over the range of the baseline amplitude.

Experimental procedure

The study will consist of a within-subjects design in two sessions separated by a washout period of at least **one week** to avoid PAS carry-over effects (Suppa et al., 2017). The two sessions will be carried out at the same moment of the day (i.e., in the morning or the afternoon). Participants will sit comfortably in a semi-reclined armchair in front of a 20" computer screen at a distance of 100 cm, with their arms relaxed on the armrests. All the experimental procedures will be the same between the two sessions, except for the PAS protocol that will be administered (i.e., PAS_{LTP} or PAS_{LTD}). As in Huber et al. (2008), we decided not to introduce a sham condition because previous PAS literature (Wischniewski & Schutter, 2016) already provides substantial evidence about the difference in the effective outcomes of the two exploited protocols, at least considering MEP modulations.

Experimental procedures are summarized in **Figure 1**. Prior to each experimental session, the motor hotspot of the right *abductor pollicis brevis* (APB) muscle (stimulation target) will be localized through neuronavigation procedures, and rMT will be determined (see **TMS**).

PAS protocols will be performed by pairing electrical median nerve stimulation with TMS over the left M1, as in the standard protocols (Stefan et al., 2000; Suppa et al., 2017; Wolters et al., 2003). Before protocol administration, the individual perceptual threshold for electrical median nerve stimulation will be estimated and set at 300% (see **Electrical nerve stimulation**). One hundred and eighty stimuli pairs will be repeated with a frequency of 0.2 Hz. **During PAS administrations**, TMS will be **always** set at 110% rMT. The two PAS protocols will differ only in terms of the ISI between the two stimulations while keeping the other parameters constant (i.e., ISI 25 ms for PAS_{LTP}; ISI 10 ms for PAS_{LTD}). The choice of the parameters was made to find a good compromise between the duration of aftereffects, the duration of the protocol itself, and optimal parameters based on two published systematic reviews investigating the effects of PAS (Suppa et al., 2017; Wischniewski & Schutter, 2016). During PAS administration, participants will be asked to count mentally the number of times the electric stimulation will be delivered (i.e., 180), thus preventing sleepiness and keeping their attention high – a critical condition for the protocol's effectiveness (Stefan, Wycislo, & Classen, 2004). To track the effects of PAS, MEPs and TEPs will be acquired before (baseline, T0), immediately after (T1), and 30 minutes after PAS end (T2 – to investigate **H3**). In the TMS-EMG block, 30 trials will be acquired. TMS-EEG blocks will consist of 150 trials each. At T0 and T1, TMS will be delivered at 110% (suprathreshold) in one block and at 90% (subthreshold) rMT in the other (to investigate **H4**). At T2, only the block at suprathreshold intensity will be recorded. In all the recording blocks acquired before and after PAS, the inter-pulse interval will be randomly jittered between 2000 and 2300 ms (Pisoni, Romero Lauro, Vergallito, Maddaluno, & Bolognini, 2018; Romero Lauro et al., 2016). TMS-EMG block will last 3 min while TMS-EEG ones will last 8 min each. During the TMS assessment, participants will be at rest and instructed to keep their eyes open, looking at a fixation cross projected on the computer screen.

The order of the experimental conditions (i.e., PAS protocols) will be counterbalanced across participants. TMS-EMG blocks will always be delivered before TMS-EEG ones.

At the end of each session, three anatomical landmarks (nasion, left and right preauricular points) and the position of the 60 EEG channels will be digitized for co-registration of the TMS-EEG data with the MRI template for offline source reconstruction. On average, an experimental session will last about 3 hours and 30 minutes.

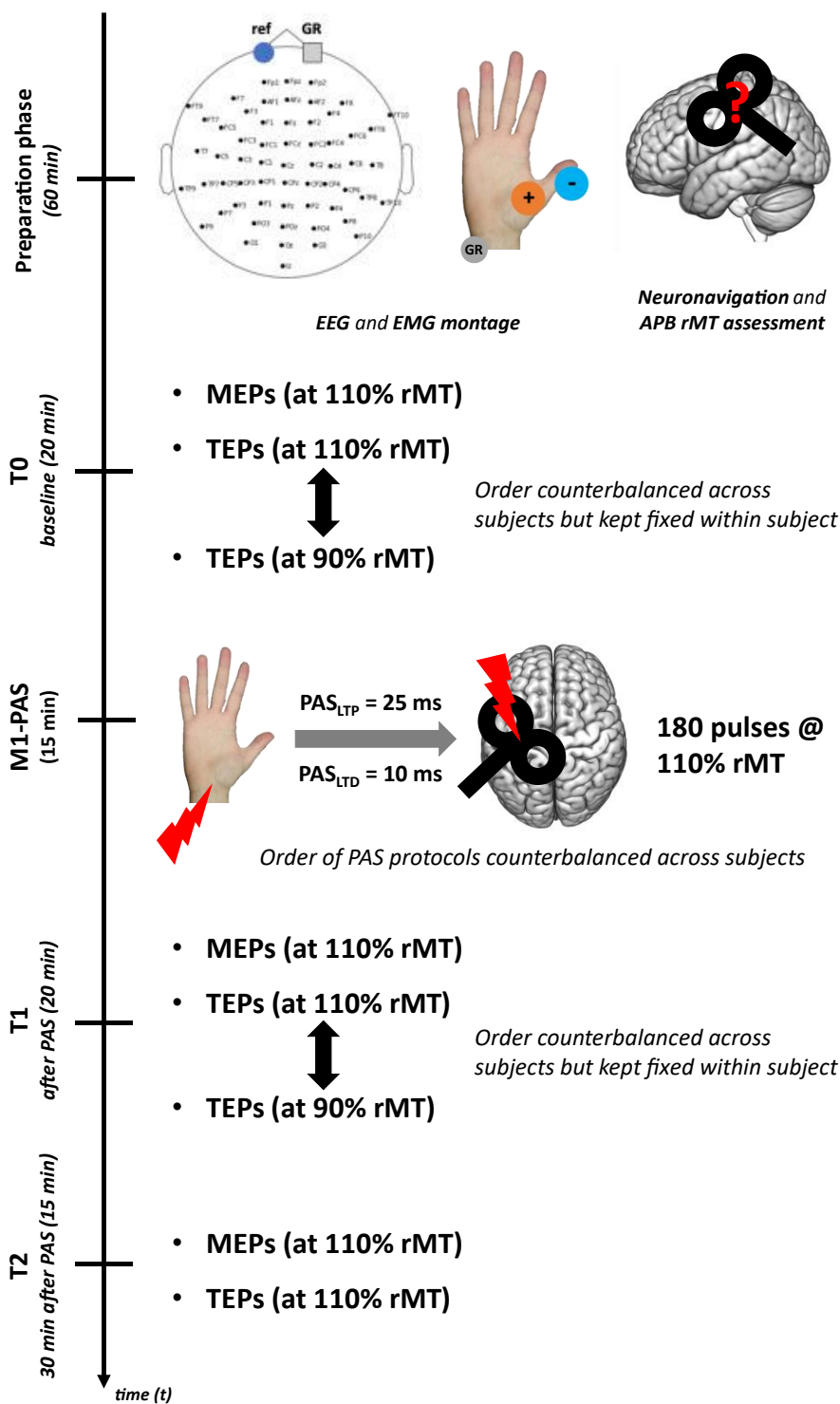


Figure 1. Experimental procedure.

Transcranial magnetic stimulation (TMS)

Single-pulse TMS will be delivered with an Eximia™ TMS stimulator (Nexstim™, Helsinki, Finland) using a biphasic focal figure-of-eight 70mm coil. The stimulation target site will be identified as the hotspot for the

right APB muscle within the left M1. The location of the stimulation target will be identified for each participant using a Navigated Brain Stimulation (NBS) system (Nexstim™, Helsinki, Finland) based on infrared-based frameless stereotaxy, allowing also accurate monitoring of the position and orientation of the coil and an online estimation of the distribution and intensity (V/m) of the intracranial electric field induced by the TMS. The coil will be placed tangentially to the scalp and tilted 45° with respect to the midline (positioned perpendicular with respect to the stimulated cortical gyrus), inducing anterior-posterior (first phase)/posterior-anterior (second phase) currents within M1. **Coil positioning will be the same during EMG and EEG blocks.**

TMS intensity will be adjusted for each participant as a percentage of the rMT. In the EEG and EMG recording sessions before and after PAS administration, as well as during PAS protocols, TMS intensity will be set at 110% rMT or 90% rMT according to the experimental condition (see **Experimental Procedure** and **H3-H4**). rMT will be preliminarily assessed in a short recording session before the experimental blocks using a parameter estimation by sequential testing (PEST) method (i.e., maximum-likelihood threshold-hunting procedure) (Awiszus, 2003; Dissanayaka, Zoghi, Farrell, Egan, & Jaberzadeh, 2018). To ensure that 90% rMT stimulation will not induce corticospinal tract response, a sanity check will be performed, in which no MEPs should be recorded in 10 consecutive trials from both APB **and a cortical adjoining muscle (i.e., first dorsal interosseus – FDI)** (Reijonen et al., 2020). If MEPs are present **in one of these muscles** at 90% rMT, **motor hotspot searching will be refined** until the sanity check is fulfilled.

Electrical nerve stimulation

Median nerve stimulation during the PAS protocols will be delivered by means of a constant current stimulator (Digitimer DS7AH, Digitimer Ltd., Hertfordshire, UK). Surface electrodes will be applied to stimulate the right-hand median nerve, exploiting a bipolar montage with the anode placed at the level of the wrist and the cathode proximal. The minimal intensity necessary to reliably elicit a sensation for each participant (based on self-report) will be recognized as the perceptual threshold. Stimulation intensity during PAS will be set at 300% of this value. The pulse width will be set at 200 µS.

EEG recordings

EEG data will be continuously acquired from a 60-channel EEG cap (EasyCap, BrainProducts GmbH, Munich, Germany) using a sample-and-hold TMS-compatible system (Nexstim™, Helsinki, Finland). Two electrodes will be placed over the forehead as ground and reference. Two additional electro-oculographic (EOG) channels will be placed near the eyes (i.e., one above the right eyebrow and the other over the left cheekbone) to detect ocular artifacts due to eye movements and blinking (Bianco, Arrigoni, Di Russo, Romero Lauro, & Pisoni, 2023; Pisoni et al., 2018; Romero Lauro et al., 2014). Noise-masking will be performed by continuously playing into earplugs an audio track created by shuffling TMS discharge noise to prevent the emergence of auditory evoked potentials (Russo et al., 2022). Noise masking volume will be individually adjusted prior to each session to fully cover TMS clicks. Electrodes' impedance will be tested prior to each experimental session and kept below 5 k Ω . EEG signals will be acquired with a sampling rate of 1450 Hz.

EMG recordings

MEPs will be recorded from the right-hand APB using Signal software (version 3.13) connected to a Digitmer D360 amplifier and a CED micro1401 A/D converter (Cambridge Electronic Devices, Cambridge, UK, www.ced.co.uk). Active electrodes (15 X 20 mm Ag-AgCl pre-gelled surface electrodes, Friendship Medical, Xi'an, China) will be placed on the right thumb with a bipolar belly-tendon montage (i.e., active electrode over the muscle belly and reference electrode over the metacarpophalangeal joint of the thumb). The ground electrode will be placed over the right head of the ulna. Only during the sanity check for 90% rMT condition, MEPs from FDI muscle will be recorded to assess the absence of MEPs also in this second muscle (active electrode will be placed over the muscle belly and reference electrode over the metacarpophalangeal joint of the index). Before data acquisition, a visual check will guarantee that background noise will not exceed 20 μ V. EMG signals will be sampled (5000 Hz), amplified, band-pass filtered (10–1000 Hz) with a 50 Hz notch filter, and stored for offline analysis. Data will be collected from 100 ms before to 200 ms after the TMS pulse (time window: 300 ms).

EEG preprocessing

EEG preprocessing will be carried out in MATLAB (MathWorks, Natick, MA, USA) using EEGLAB (Delorme & Makeig, 2004) and TESA toolbox (Rogasch et al., 2017) functions. First, raw data will be down-

sampled to 725 Hz. The continuous signal will be re-referenced using an average reference, segmented in epochs starting 800 ms pre- and ending 800 ms post-TMS pulse, and baseline-corrected between -300 and -50 ms before TMS pulse. Single trials with excessive artifacts will be rejected by visual inspection. The source-estimate-utilizing noise-discarding algorithm (SOUND, see Mutanen et al., 2018) implemented in TESA (Rogasch et al., 2017) will be applied to attenuate extracranial noise coming from bad channels, exploiting a 3-layer spherical model with default parameters ($\lambda = 0.1$, as in Mutanen et al., 2018). **Independent Component Analysis (FastICA, pop_tesa_fastica, 'tanh' contrast) will be performed after Principal Component Analysis (PCA) compression to 30 components (pop_tesa_pcacompress). FastICA will be applied to remove blinks, eye movements, residual electrical artifacts, and spontaneous muscular activity by visual inspection (Hernandez-Pavon et al., 2012).** To suppress TMS-evoked muscle artifacts in the first 50 ms post-TMS, a semiautomatic signal space projection method for muscle artifact removal (SSP-SIR) will be applied (Mutanen et al., 2016). Epochs will be band-pass filtered from 1 to 70 Hz and band-stop filtered from 48 to 52 Hz using a 4th-order Butterworth filter.

TEPs extraction

To narrow our investigation to the dynamics of the local circuitry of the left M1, we will compute the average of TEPs across a specified region of interest (ROI), including electrodes under the stimulation coil and in correspondence with the scalp site of the cortical target, approximately C1, C3, C5, CP3, and FC3 (e.g., Costanzo et al., 2023). The electrodes to be included in the ROI will be verified by visual inspection of the greatest response amplitude after the TMS pulse **in the grand average of all participants. Then, the ROI will be kept fixed among the participants.** Following this, we will extract P30, P60, and N100 TEP components by averaging the individual amplitudes and extracting the positive and negative peaks in the selected time intervals: 20–35 ms (P30), 55–70 ms (P60), and 90–130 ms (N100). These time intervals were chosen according to the available literature on the M1-TEP components elicited by both suprathreshold and subthreshold stimulations (Gordon, Desideri, Belardinelli, Zrenner, & Ziemann, 2018; Lioumis et al., 2009; Premoli, Castellanos, et al., 2014).

EMG preprocessing

Concerning EMG preprocessing, MEPs will be analyzed offline using Signal software (version 3.13), following the standard preprocessing pipeline used in our laboratory (Guidali, Picardi, Franca, Caronni, & Bolognini, 2023). At first, trials with artifacts (muscular or background noise) exceeding 200 μV in the 100 ms before the TMS pulse will be automatically excluded from the analysis. Then, MEP peak-to-peak amplitude will be calculated in each trial in the time window between 5 ms and 60 ms from the TMS pulse. Trials in which MEP amplitude will be smaller than 50 μV will be excluded from the following analysis.

Planned statistical analysis

For our *positive control* condition (**H0**), MEP amplitude data will be analyzed through planned comparisons using robust statistics (i.e., Yuen's trimmed mean paired sample t-test, one-tailed) (Mair & Wilcox, 2020; Yuen, 1974); in detail, according to our *a priori* hypothesis, we will test that, for PAS_{LTP} , MEP amplitude is higher after the administration of the protocol (T1) concerning the baseline (T0); for PAS_{LTD} , we expected the reversed pattern (i.e., MEP amplitude lower than T0 after the PAS administration).

For **H1**, PAS effects on TEP peak amplitude (i.e., P30 and P60) will be separately analyzed through 2 X 2 within-subjects rmANOVA with factors 'PAS protocol' (PAS_{LTP} , PAS_{LTD}) and 'Time' (T0, T1).

For **H2**, PAS_{LTD} effects on N100 will be assessed through robust statistics exploiting one-tailed Yuen's trimmed mean paired sample t-test (Mair & Wilcox, 2020; Yuen, 1974), comparing N100 amplitude before (T0) and after (T1) the administration of PAS_{LTD} .

For **H3**, the temporal profile of PAS aftereffects on MEP, P30, P60, and N100 amplitude will be investigated through 3 X 2 within-subjects rmANOVA with factors 'PAS protocol' (PAS_{LTP} , PAS_{LTD}) and 'Time' (T0, T1, T2).

Finally, for **H4**, possible effects of supra- or subthreshold intensity on P30 and P60 amplitude in the PAS_{LTP} will be investigated. Given the rationale of our *a priori* hypothesis (see **Introduction**), this analysis will be conducted only if **H1** will show significant modulation of P60 amplitude after PAS_{LTP} administration. Here, for each component, we will calculate the ratio of T1 peak amplitude over T0. Then, 'post-pre amplitude' ratio will be used as dependent variable in a 2 X 2 within-subjects rmANOVA with factors 'Intensity' (90%, 110%) and 'Component' (P30, P60).

In all our rmANOVAs, significant main effects and interactions will be further explored with post-hoc tests by applying the Tukey's correction for multiple comparisons. If data sphericity is not confirmed by Mauchly's test, the Greenhouse–Geisser correction will be applied. Partial eta-squared (η_p^2 – for rmANOVAs) and Cohen's d (for t-tests) will be reported as effect size values. For each variable, the mean \pm standard error (SE) will be reported. The normality of our data distributions will be tested using the Shapiro-Wilks test and Q-Q plot assessment. If normality is not achieved, to make the distribution closer to normality, we will transform the raw data with three commonly used transformations for continuous variables: (a) square root [i.e., $\sqrt{\text{raw data}}$], (b) base-ten logarithmic [i.e., $\log_{10}(\text{raw data})$], and (c) inverse transformation [i.e., $1/(\text{raw data})$]. To account for possible negative values, as well as values between 0 and 1, when applying these transformations, we add a constant to the raw data values, thus anchoring the minimum of our distribution(s) to 1 (Osborne, 2010). Then, we will select among these three transformations the one showing the best fit to a normal distribution (i.e., the transformed distribution presents values of an excess kurtosis between -2 and 2 and skewness between -1 and 1; the distribution which values will fall into these ranges and will be closer to 0, will be selected – George & Mallery, 2019). Statistical analyses are planned to be performed using the Jamovi software (The Jamovi Project, 2023), R Studio (R Core Team, 2020), and Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011).

Question	Hypothesis	Sampling plan	Analysis Plan	Rationale for deciding the sensitivity of the test for confirming or disconfirming the hypothesis	Interpretation given different outcomes	Theory that could be shown wrong by the outcomes
<i>Ho (Positive control). Do PAS protocols effectively modulate the corticospinal excitability (as indexed by MEP amplitude)?</i>	<p>PAS_{LTP}: post > pre PAS_{LTD}: post < pre</p> <p>Compared to baseline levels, PAS_{LTP} should increase MEP amplitude immediately after the stimulation. Conversely, PAS_{LTD} should reduce MEP amplitude after protocol administration.</p>	<p>[All power analyses were conducted using the software G*Power 3.1 (Faul et al., 2009), with an alpha of 0.02 and a power of 0.9]</p> <p>In a meta-analysis by Wischnewski et al. (2016), the authors found a significant potentiation of MEPs amplitude right after PAS_{LTP} administration (d = 1.44) and MEP depression (d = 2.04) after PAS_{LTD}. We focused on the smaller effect size between the two. To account for potential publication bias (Anderson et al., 2017), we have considered a smaller Cohen's d value (d = 0.7) for power analysis. The estimated sample for a one-tailed dependent sample t-test resulted in 25 participants.</p>	<p>MEP amplitude data will be analyzed through planned comparisons using robust statistics (i.e., Yuen's trimmed mean paired sample t-test, one-tailed) (Mair and Wilcox, 2020; Yuen, 1974)</p>	<p>We based our power analysis on the meta-analysis by Wischnewski et al. (2016), in which the authors evaluated the effects of PAS_{LTP} across 70 experiments performed in 60 studies and found a significant potentiation of MEPs amplitude right after PAS_{LTP} administration (d = 1.44). The analysis of 39 PAS_{LTD} studies reported MEP depression (d = 2.04). We focused on the smaller effect size between the two and considered half of the d value to account for potential publication bias (Anderson et al., 2017).</p>	<p>Compared to the baseline, a significant increase in MEP amplitude after PAS_{LTP} and a decrease following PAS_{LTD} will be interpreted as an effective induction of LTP and LTD effects within the motor system and a replication of the previous literature. Conversely, if post-PAS MEP measurements do not differ from the baseline or display an opposite pattern (PAS_{LTP}: post < pre; PAS_{LTD}: post > pre), the obtained results will be interpreted as a non-replication of previous findings.</p>	-
<i>H1. Do PAS protocols modulate early M1-TEP amplitude components (P30 and P60) reflecting local cortical excitability?</i>	<p>PAS_{LTP}: post > pre PAS_{LTD}: post < pre</p> <p>Compared to baseline levels, PAS_{LTP} should increase P30 and P60 amplitude immediately</p>	<p>We considered the significant interaction between 'Condition' (real vs. sham) and 'Time' (pre vs. post) (F_{1,15} = 8.469, p = 0.011, partial eta-squared –</p>	<p>PAS effects on P30 and P60 amplitude will be separately analyzed through 2 X 2 within-subjects rmANOVA with factors 'PAS protocol'</p>	<p>We based the power analysis on the study by Costanzo et al. (2023), which is, to date, the only published report of a TMS-EEG experiment evaluating the effects of a</p>	<p>Compared to the baseline, a significant increase in P30 and P60 amplitude after PAS_{LTP} will be interpreted as an upregulation of local excitability within the motor system at the cortical level, thus, an</p>	-

	<p>after the PAS administration (as in Costanzo et al., 2023). Conversely, PAS_{LTD} should reduce P₃₀ and P₆₀ amplitude after protocol administration.</p>	<p>$\eta_p^2 = 0.361$) reported in Costanzo et al., 2023 for sample size estimation. To account for potential publication bias (Anderson et al., 2017), we have considered half of the reported η_p^2 (i.e., 0.18) for rmANOVA power analysis. The estimated sample resulted in 10 participants.</p>	<p>(PAS_{LTP}, PAS_{LTD}) and 'Time' (T₀, T₁).</p>	<p>PAS_{LTP} protocol on specific M1-TEP components. We considered the reported significant interaction between 'Condition' (real vs. sham) and 'Time' (pre vs. post) ($F_{1,15} = 8.469$, $p = 0.011$, $\eta_p^2 = 0.361$) for sample size estimation. To account for potential publication bias (Anderson et al., 2017), we have considered half of the reported η_p^2 (i.e., 0.18) for rmANOVA power analysis.</p>	<p>effective induction of LTP and a replication of the previous literature. On the same line, we expect to find the opposite pattern after the induction of PAS_{LTD} which will be interpreted as a downregulation of local cortical excitability. Alternatively, if we do not observe early TEP amplitude modulation after PAS_{LTD}, this will not be considered a sensitive measure of LTD induction. Finally, if post-PAS TEP measurements do not differ from the baseline or display a different pattern (e.g., PAS_{LTP}: post < pre; PAS_{LTD}: post > pre), the obtained results will be interpreted in light of the methodological differences with the previous study (e.g., PAS parameters, TEP acquisition, data analysis pipeline), and H₅ will not be tested.</p>	
<p>H2. Does PAS_{LTD} protocol modulate a late M1-TEP amplitude component reflecting GABAergic transmission (N₁₀₀)?</p>	<p>Compared to baseline levels, PAS_{LTD} should increase N₁₀₀ amplitude (i.e., greater negativity) immediately after the protocol administration.</p>	<p>We considered the difference in M1-TEP N₁₀₀ amplitude over fronto-central electrodes of $1.88 \pm 0.66 \mu V$ ($d = 2.85$) reported by Casula and coworkers (2014) after inhibitory rTMS administration. To account for potential publication bias, we have considered half of the reported d (i.e., $d = 1.42$) for our power analysis. Here, the estimated sample size is 10 participants.</p>	<p>PAS_{LTD} effects on N₁₀₀ amplitude will be analyzed through planned comparisons (T₀ vs. T₁) using robust statistics (i.e., Yuen's trimmed mean paired sample t-test, one-tailed) (Mair and Wilcox, 2020; Yuen, 1974)</p>	<p>In the absence of a similar comparison in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008), we based our estimation on the work by Casula et al. (2014) which found M1-TEP N₁₀₀ enhancement after low-frequency (i.e., inhibitory) repetitive TMS. The authors reported a difference in N₁₀₀ amplitude over fronto-central electrodes of $1.88 \pm 0.66 \mu V$ corresponding to a d of 2.85 (Casula et al., 2014). As for the previous estimations, to account</p>	<p>Compared to the baseline, a significant increase in N₁₀₀ amplitude after PAS_{LTD} will be interpreted as an upregulation of GABAergic activity within the motor system, i.e., an effective induction of LTD. If post-PAS N₁₀₀ does not differ from the baseline or display different patterns (e.g., PAS_{LTD}: post < pre), our hypothesis will not be confirmed and the results will be interpreted in the light of available literature.</p>	-

				for potential publication bias, we have considered half of the reported d (i.e., $d = 1.42$) for our power analysis.		
H3. Does PAS-induced plasticity fade away over time?	We hypothesize that induced plasticity fades away about 30 minutes after the end of the protocol, likely for both PAS _{LTP} and PAS _{LTD} .	We considered the work by Costanzo and colleagues (2023), reporting a significant main effect of 'Time' ($F_{2,30} = 4.679, p = 0.047, \eta_p^2 = 0.238$) after PAS _{LTP} administration. We have considered half of the reported η_p^2 (i.e., $\eta_p^2 = 0.119$) for our rmANOVA power analysis. The estimated sample resulted in 18 participants.	The temporal profile of PAS aftereffects on MEP, P ₃₀ , P ₆₀ and N ₁₀₀ amplitude will be separately investigated through 3 X 2 within-subjects rmANOVA with factors 'PAS protocol' (PAS _{LTP} , PAS _{LTD}) and 'Time' (T ₀ , T ₁ , T ₂).	For our sample size estimation, we considered the work by Costanzo and colleagues (2023), reporting a significant main effect of factor 'Time' ($F_{2,30} = 4.679, p = 0.047, \eta_p^2 = 0.238$) after PAS _{LTP} administration and exploiting three timepoints as in our study. As for the previous estimations, to account for potential publication bias, we have considered half of the reported η_p^2 (i.e., $\eta_p^2 = 0.119$) for our power analysis.	If plastic effects are not sustained over time, as we hypothesize given previous literature, data recorded after 30 minutes will statistically differ from data collected immediately after PAS administration but will not differ from baseline. Alternatively, if PAS effects are sustained over time, data recorded after 30 minutes will not statistically differ from data collected after PAS administration, although significantly different from baseline. In this case, our a-priori hypothesis will not be confirmed. Differential temporal patterns between PAS protocols will be interpreted in light of Ho-H1 results.	-
H4. Does the MEP-related reafferent processing differently influence P₃₀ and P₆₀ amplitude while tracking the effects of PAS_{LTP}? <i>(This hypothesis will be tested only depending on H1 results; i.e., P₆₀ after PAS_{LTP} is effectively modulated)</i>	If P ₆₀ amplitude modulation is dependent of the reafferent signal, we expect that the presence of MEPs (in the suprathreshold stimulation condition) will lead to a greater amplitude enhancement of this component compared to the noMEP condition (subthreshold TMS). For P ₃₀ , no difference should be found between supra- and subthreshold intensities	In the absence of previous studies, we hypothesized a medium effect size ($\eta_p^2 = 0.06$). The power analysis resulted in 30 participants.	For each component (i.e., P ₃₀ and P ₆₀), we will calculate the ratio of T ₁ peak amplitude over T ₀ . Then, pre-post amplitude ratio will be used as dependent variable in a 2 X 2 within-subjects rmANOVA with factors 'Intensity' (90%, 110%) and 'Component' (P ₃₀ , P ₆₀).	in the absence of a comparison between supra- vs. subthreshold TEPs in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008) or studies investigating this question with a pre- vs. post-intervention experimental design, we run a 2 X 2 rmANOVA power analysis hypothesizing a medium effect size ($\eta_p^2 = 0.06$).	If the 'Intensity' X 'Component' interaction is statistically significant, this will be interpreted as a differential influence of MEP reafference on the two examined components. In detail, if P ₆₀ pre-post amplitude ratio will be significantly greater in the suprathreshold condition, while P ₃₀ pre-post ratio should not differ between the two intensities. Alternatively, a significant main effect of 'Intensity' without a significant interaction will be discussed as a general increase in response magnitude due to a higher stimulation intensity. Other modulation patterns will be interpreted in light of the results	

					found in the previous hypothesis (H₀ , H₁).	
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Table 1. Study design.

DATA AVAILABILITY STATEMENT

Data and code of the study will be made available at a recognized online repository at the moment of Stage 2 submission. Registered Report snapshot and Stage 1 versions of the manuscript can be found at: <https://osf.io/48fh3/>

CRedIT AUTHOR CONTRIBUTION (Stage 1)

Eleonora Arrigoni: conceptualization, methodology, data curation, software, visualization, writing – original draft

Nadia Bolognini: methodology, supervision, writing – review & editing

Alberto Pisoni: methodology, supervision, validation, resources, writing – review & editing

Giacomo Guidali: conceptualization, methodology, validation, data curation, visualization, writing – original draft

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