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 characterize the neurophysiological substrates better, grounding the effectiveness of such protocol. This investigation will provide evidence about the specificity of early transcranial-evoked potential (TEP) components in reflecting changes of M1 functional activity 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., 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. Thus, the spatiotemporal profile of early evoked cortical responses will be deeply investigated.

Our study aims to foster evidence about using TMS-EEG biomarkers to track complex plastic changes induced in the human brain exploiting 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 potentials (TEPs)

INTRODUCTION

Paired associative stimulation (PAS) is a class of non-invasive brain stimulation protocols 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 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, Iliać, 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}) (e.g., 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 (e.g., 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; Wischnewski & Schutter, 2016), and modified versions targeting other cortical areas/networks than M1 and the motor system arose in recent years (e.g., Bevilacqua, Huxlin, Hummel, & Raffin, 2023; Borgomaneri et al., 2023; Casarotto et al., 2023; Di Luzio, Tarasi, Silvanto, Avenanti, & Romei, 2022; 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 (e.g., 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 evaluated the effectiveness of the M1-PAS-induced plasticity within the motor system by focusing, as primary outcomes, on corticospinal excitability (i.e., motor-evoked potentials – MEPs) or behavioral measures (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 effective connectivity before and after non-invasive brain stimulation, leveraging the sensitivity of TMS-evoked potentials (TEPs) to track global changes induced by neuromodulation (for reviews, see: Cruciani et al., 2023; Hernandez-Pavon 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 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 highlighted 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 that 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 evidence 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).

Given these premises, in the present study, we aim to deepen the cortical underpinnings of M1-PAS-induced plasticity exploiting TMS-EEG. This investigation is indeed crucial to derive cortical biomarkers of plastic changes in the human brain. To this end, our study aims to better characterize 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) 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 (Wischnewski & Schutter, 2016). Namely, MEPs recorded after PAS_{LTP} are 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 have effectively induced associative plasticity 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 hypothesize that P30 and P60 will show an amplitude reduction. Notably, these two components are often used as biomarkers of cortical excitability in studies aimed at assessing the effects of non-invasive neuromodulation techniques inducing LTD/LTP-like phenomena within the motor system through TMS-EEG (for a review, see: Cruciani et al., 2023).

In detail, P30 is thought to reflect fast excitatory mechanisms within M1 local circuitry (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 iTBS-induced changes in N15-P30 TEP complex and MEP amplitude were significantly correlated (Gedankien, Fried, Pascual-Leone, & Shafi, 2017).

On the other hand, P60 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 the 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 will be 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 is that Costanzo et al. (2023) found no significant modulation of the N100 after PAS_{LTP}. So, given the controversial literature on N100 modulations after the administration of excitatory TMS protocols (e.g., Bai, Zhang, & Fong, 2021; Chung et al., 2019; Desforges et al., 2022; Goldsworthy et al., 2020), no analysis on PAS_{LTP}-N100 effects will be registered.

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; Wischnewski & 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 (i.e., P60; e.g., Fecchio et al., 2017; Komssi, Kähkönen, & Ilmoniemi, 2004) with respect to early components (i.e., P30; e.g., Gordon, Desideri, Belardinelli, Zrenner, & Ziemann, 2018; Petrichella, Johnson, & He, 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 PAS_{LTP} (Costanzo et al., 2023), we hypothesize that, in such a protocol, the change in P60 magnitude could be overestimated due to the involvement of MEP reafference (**H4**). Hence, to rule out this hypothesis and provide more detailed information for the overall interpretation of the results, 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). Suppose the reafferent signals have a major impact on P60 amplitude modulation. In that case, we expect that, compared to P30 (which is too early and allegedly unaffected by MEP reafference), 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). Given the rationale behind this fourth hypothesis, we will test it only if a significant modulation of P60 is found in **H1**.

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, deepening the spatiotemporal patterns of M1-TEPs after the administration of excitatory and inhibitory M1-PAS protocols (see **Study Table** for all our *a priori* hypotheses and related planned analysis).

---------- *Insert Study Table 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 before 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 has received approval from the local Ethics Committee (protocol number 797). 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 (**Study Table**). 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*

For the *positive control* of our study, we based our sample size estimation on a meta-analysis by Wischnewski and colleagues (2016). Here, 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 protocol 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 this M1-PAS version ($d = 2.04$). 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) <u>*H1: Effects of PAS protocols on early positive TEP components (P30 and P60)*</u>

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, 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 to account for potential publication bias. The estimated sample resulted in 10 participants.

c) <u>*H2: Effects of PAS_{LTD} on the N100*</u>

Based on previous literature about LTD and M1-TEPs (Casula et al., 2014), and 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 ± 0.66 μV corresponding to a Cohen's *d* of 2.85 (Casula et al., 2014). As for the previous estimations, we have considered half of the reported *d* (i.e., $d = 1.42$) for our power analysis to account for potential publication bias. Here, the estimated sample size for a one-tailed dependent sample t-test is 10 participants.

d) *H3: Temporal evolution of induced plasticity*

Here, we will evaluate the temporal evolution of the two PAS protocols. 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 timepoints similar to the ones of our study. As for the previous estimations, we have considered half of the reported η_p^2 (i.e., $\eta_p^2 = 0.119$) for our rmANOVA power analysis to account for potential publication bias. 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, our study will examine P30 and P60 modulations elicited by supra- and subthreshold TMS pulses after PAS_{LTP}. Considering only the excitatory version of the M1-PAS, in the absence of comparison between supra- *vs.* subthreshold TEPs in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008), as well as in 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, additional participants will be recruited to make up for the possibility of dropouts or outliers (see **Exclusion criteria**) 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 (score below 0), presented contraindications to TMS according to Rossi et al.'s (2021) 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 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 80 TMS-EEG trials survive after trial rejection during preprocessing in at least one of the recording blocks.

g) TMS-EEG cleaned data have a 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 already provides substantial evidence about the difference in the effective outcomes of the two exploited protocols, at least considering MEP modulations (Wischnewski & Schutter, 2016).

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 electric stimulation during PAS will be set at 300% of this value (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 delivered 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 of 25 ms for PAS_{LTP}; ISI of 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; Wischnewski & 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 120 trials each. Here, 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 3000 and 4000 ms. During TMS-EMG blocks, TMS will be delivered with the EEG cap on and with the same conditions (i.e., noise masking applied) and parameters of TMS-EEG recordings – see **TMS** and **EMG recording** for further details. The TMS-EMG block will last 3 minutes, while the TMS-EEG ones will last 8 minutes 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 sessions (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. On average, an experimental session will last about 3 hours and 30 minutes.

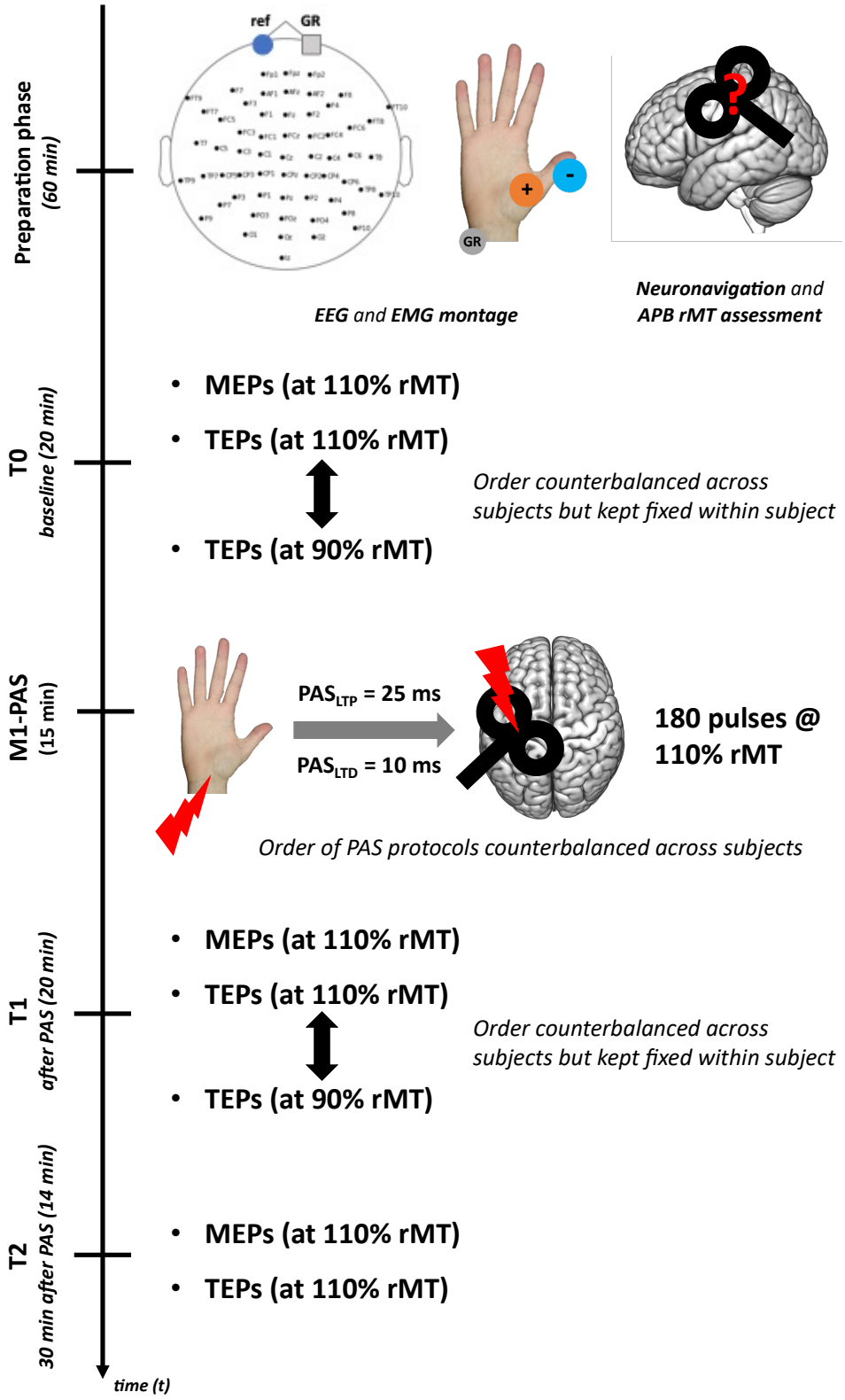

Figure 1. *Experimental procedure.*

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 and in each session as a percentage of the rMT. 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). A sanity check will ensure that 90% rMT stimulation will not induce corticospinal tract response: no MEP 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. Once the individual's rMT value is determined, TMS intensity in the TMS-EEG blocks will be set at 110% rMT or 90% rMT according to the experimental condition (see **Figure 1** and **H3-H4**). Considering the aim of TMS-EMG blocks (i.e., **H0)**, MEPs will be recorded only at 110% rMT. Finally, during both PAS protocols, TMS will always be administered at 110% rMT.

Electrical nerve stimulation

Median nerve stimulation during the PAS protocols will employ 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 recording

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 (as done in, e.g., Bianco, Arrigoni, Di Russo, Romero Lauro, & Pisoni, 2023; Pisoni, Romero Lauro, Vergallito, Maddaluno, & Bolognini, 2018; Romero Lauro et al., 2014). Noise masking will be performed by continuously playing an audio track into earplugs 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 before each session to cover TMS clicks fully. Electrodes' impedance will be tested prior to each experimental session and kept below 5 kΩ. EEG signals will be acquired with a sampling rate of 1450 Hz.

EMG recording

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). 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 the FDI muscle will be recorded to assess the absence of corticospinal responses 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 μV. During TMS-EMG, participants will also have noise masking to keep all recording conditions constant

between EMG and EEG blocks. 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). A semiautomatic signal space projection method for muscle artifact removal (SSP-SIR) will be applied to suppress TMS-evoked muscle artifacts in the first 50 ms post-TMS (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 4^{th}-order Butterworth filter.

TEPs extraction

To narrow our investigation to the dynamics of left M1 local circuitry, 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 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 (e.g., Gordon et al., 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 (e.g., 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, trimming level: 20%) (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 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, the 'post-pre amplitude' ratio will be used as the 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 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 ± standard error (SE) will be reported. Statistical significance will be set at $p < 0.02$. 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., $\log_{10}$(raw data)], and (*c*) inverse transformation [i.e., 1/(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 *[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]*	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
H0 (Positive control). Do PAS protocols effectively modulate corticospinal excitability (as indexed by MEP amplitude)?	PAS $_{LTP}$: post > pre PAS $_{LTD}$: post < pre Compared to baseline levels, PAS_{LTP} should increase MEP amplitude immediately after the stimulation. Conversely, PAS_{LTD} should reduce MEP amplitude after protocol administration.	In a meta-analysis by Wischnewski et al. (2016), the authors found a significant potentiation of MEP amplitude right after PAS_{LTP} administration (d = 1.44) and a significant 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.	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).	We based our power analysis on the meta-analysis by Wischnewski and coworkers (2016). Here, 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. On the other hand, the analysis of 39 PAS_{LTD} studies reported MEP depression.	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.	If **H0** is not confirmed, it will suggest that our PAS_{LTP} and/or PAS_{LTD} protocols do not induce plastic changes detectable at a corticospinal level. This evidence would argue the effectiveness of PAS protocols, at least at the population level and on MEPs. Nevertheless, such finding will not *a priori* exclude the absence of effects on TEPs – and thus the ineffectiveness of our protocol, given the evidence that MEPs and TEPs could frame different facets of motor system excitability (Biabani, Fornito, Coxon, Fulcher, & Rogasch, 2021; Guidali, Zazio, et al., 2023). Hence, we will still explore TEPs (i.e., **H1-H4** hypothesis) and set up the discussion of our results accordingly.
H1. Do PAS protocols modulate early M1-TEP amplitude	PAS $_{LTP}$: post > pre PAS $_{LTD}$: post < pre	We considered the significant interaction between 'Condition' (real vs. sham) and	PAS effects on P30 and P60 amplitude will be separately	We based the power analysis on the study by Costanzo and colleagues (2023),	Compared to the baseline, a significant increase in P30 and P60 amplitude after PAS_{LTP}	Firstly, if **H1** is not confirmed, previous evidence found on PAS_{LTP}-induced

components (P30 and P60) reflecting local cortical excitability?	Compared to baseline levels, PAS_{LTP} should increase P30 and P60 amplitude immediately after the PAS administration (as in Costanzo et al., 2023). Conversely, PAS_{LTD} should reduce P30 and P60 amplitude after protocol administration.	'Time' (pre vs. post) ($F_{1,15}$ = 8.469, p = 0.011, partial eta-squared – η_p^2 = 0.361) reported in Costanzo et al. (2023) for sample size estimation. To account for potential publication bias, 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.	analyzed through 2 X 2 within-subjects rmANOVA with factors 'PAS protocol' (PAS_{LTP}, PAS_{LTD}) and 'Time' (T0, T1).	which is, to date, the only published report of a TMS-EEG experiment evaluating the effects of a PAS_{LTP} protocol on specific M1-TEP components. We considered the reported significant interaction between 'Condition' (real vs. sham) and 'Time' (pre vs. post) for sample size estimation.	will be interpreted as an upregulation of local excitability within the motor system at the cortical level, i.e., effective induction of LTP and 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 **H4** will not be tested.	modulations (i.e., Costanzo et al., 2023) will not be confirmed and replicated. Secondly, this would suggest that P30 and/or P60 might not be reliable measures for detecting PAS-induced LTP/LTD.
H2. Does PAS_{LTD} protocol modulate a late M1-TEP amplitude component reflecting	Compared to baseline levels, PAS_{LTD} should increase N100 amplitude (i.e., greater negativity)	We considered the difference in M1-TEP N100 amplitude over fronto-central electrodes of 1.88 ± 0.66 μV (d = 2.85)	PAS_{LTD} effects on N100 amplitude will be analyzed through planned comparisons (T0	In the absence of a similar comparison in previous TMS-EEG PAS studies (Costanzo et al., 2023; Huber et al., 2008), we based	Compared to the baseline, a significant increase in N100 amplitude after PAS_{LTD} will be interpreted as an upregulation of	If **H2** is not confirmed, the role of the N100 as a marker of PAS_{LTD} effects within the motor system will be critically discussed and framed

GABAergic transmission (N100)?	immediately after the protocol administration.	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.	*vs.* T1) using robust statistics (i.e., Yuen's trimmed mean paired sample t-test, one-tailed) (Mair and Wilcox, 2020; Yuen, 1974)	our estimation on the work by Casula et al. (2014), which found M1-TEP N100 enhancement after low-frequency repetitive TMS (Casula et al., 2014).	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.	within available literature on this TEP component and related confounding factors (e.g., somatosensory/auditory artifacts).
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, η_p^2 = 0.238) after PAS_{LTP} administration. We have considered half of the reported η_p^2 (i.e., η_p^2 = 0.119) for our rmANOVA power analysis. The estimated sample resulted in 18 participants.	The temporal profile of PAS aftereffects on MEP, P30, P60, and N100 amplitude will be separately investigated through 3 X 2 within-subjects rmANOVA with factors 'PAS protocol' (PAS_{LTP}, PAS_{LTD}) and 'Time' (T0, T1, T2).	We based our sample size calculation on the work by Costanzo et al. (2023), reporting a significant main effect of the factor 'Time' after PAS_{LTP} administration and exploiting time points similar to the ones in our study.	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 **H0-H1** results.	If **H3** is not confirmed, we can assume that M1-PAS plastic effects have a longer duration, extending beyond twice the time of the protocol administration. This information could then be useful to better characterize the temporal profile of LTP-/LTD-induced plasticity by PAS protocols and inform future studies that require the exploitation of such plastic effects for wider time windows.
H4. Does the MEP-related reafferent	If P60 amplitude modulation is	We hypothesized a medium effect size	For each component (i.e.,	In the absence of a comparison between	If the 'Intensity' X 'Component' interaction	If **H4** is not confirmed, our results will not

processing influence P30 and P60 amplitude differently while tracking the effects of PAS_{LTP}? ***(This hypothesis will be tested only depending on H1 results; i.e., M1-TEP P60 after PAS_{LTP} is effectively modulated)***	dependent on 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 condition where no MEP is recorded (subthreshold TMS). For P30, no difference should be found between supra- and subthreshold intensities	(η_p^2 = 0.06) for our planned 2 X 2 rmANOVA. The power analysis resulted in 29 participants.	P30 and P60), we will calculate the ratio of T1 peak amplitude over T0. Then, the pre-post amplitude ratio will be used as the dependent variable in a 2 X 2 within-subjects rmANOVA with factors 'Intensity' (90%, 110%) and 'Component' (P30, P60).	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 (η_p^2 = 0.06).	is statistically significant, this will be interpreted as a differential influence of MEP reafference on the two examined components. In detail, if the P60 pre-post amplitude ratio is significantly greater in the suprathreshold condition, the P30 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**).	corroborate previous studies indicating that M1-TEP components after 50-60 ms (i.e., P60) are influenced by reafferent processing (e.g., Gordon et al., 2018; Petrichella et al., 2017). This evidence could then be useful to inform study designs in which M1-TEPs are planned to be exploited as plasticity markers within the motor system, informing on the spurious modulation of supra-threshold stimulation – and the reafferent processing – on the recorded signal.

Table 1. Study design.

DECLARATION OF INTEREST

The authors declare no competing interests.

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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