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# Recent Progress and Emerging Perspectives on How Technical Parameters of Transcranial Magnetic Stimulation Shape Cortical Measures Derived from Concurrent Electroencephalography

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## ABSTRACT

**Objectives:** Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) offers a unique opportunity to probe cortical dynamics by capturing transcranial magnetic stimulation (TMS)-evoked potentials (TEPs). Although TEPs are increasingly used as biomarkers of cortical function, their physiological interpretation is complicated by substantial methodologic variability across studies. Among the critical factors that influence TEPs is the often arbitrary choice of technical parameters for TMS administration, such as pulse waveform, width, or coil orientation, which determine the direction of the induced current in the brain, with essential implications for both basic and clinical research.

**Materials and Methods:** We conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant systematic review that collated evidence from studies manipulating TMS pulse waveform, pulse width, or current direction in healthy participants and explored the effects of these methodologic modulations on TEPs. Our search on Scopus, Web of Science, and MEDLINE databases identified 9 TMS-EEG studies that systematically evaluated the impact of these parameters on cortical measures recorded concurrently with EEG.

**Results:** Across the available literature, the direction of the TMS-induced current exerts the most decisive influence on TEPs, particularly for early components (< 50 milliseconds), supporting the selective activation of distinct circuits and networks when different coil orientations are used to target the same brain site. The pulse waveform further modulated these direction-specific effects, with monophasic pulses exhibiting greater specificity in activation patterns than biphasic ones. Even if this investigation was primarily conducted within the motor system, similar parameter-dependent changes were also observed when premotor and associative regions were stimulated, affecting TEP morphology, oscillatory activity, and functional connectivity.

**Conclusions:** Findings from these studies underscore the critical role of TMS technical parameters in shaping cortical responses, highlighting the need to carefully consider these variables to optimize neurostimulation/modulation protocols targeting specific cortical networks or pathways and more broadly to improve the reproducibility of TMS aftereffects.

**Keywords:** current direction, electroencephalography, pulse waveform, transcranial magnetic stimulation, TMS-evoked potentials

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## INTRODUCTION

Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) is a powerful noninvasive technique for probing cortical dynamics, allowing the investigation of the brain's immediate response to transcranial magnetic stimulation (TMS), that is, TMS-evoked potentials (TEP).<sup>1–3</sup> TEPs are sensitive to the subject's cognitive and clinical state, offering insights into functional brain organization during task performance and potential biomarkers for pathological conditions.<sup>4–6</sup> For instance, alterations in TEP morphology have been observed across different neurological and psychiatric disease states and stages, including, for example, depression, dementia, schizophrenia, or borderline personality disorder.<sup>7–13</sup>

However, despite their increasing utility, a major obstacle for the interpretation and reproducibility of TEP findings remains the substantial methodologic heterogeneity across TMS-EEG studies.<sup>3</sup> From the EEG signal perspective, factors such as the criteria adopted for artifact identification and rejection, in addition to the choice of preprocessing and analysis pipelines, can substantially affect the spatiotemporal characteristics of TEPs.<sup>14–16</sup> From the TMS perspective, key methodologic variables that tend to influence TEP reliability include stimulation site location—a particularly challenging issue when targeting cortical regions other than the primary motor cortex (M1)—and stimulation intensity (eg, based on motor threshold or the magnitude of early TEP components).<sup>17,18</sup> In addition, and constituting the primary focus of the present review, TMS technical parameters such as pulse waveform and pulse width, in addition to the direction of the currents induced in the brain by stimulation, have been shown to critically shape TEPs.<sup>19,20</sup>

Historically, research on the impact of technical parameters on TMS output has been focused on the motor system.<sup>21</sup> Indeed, TMS over M1 directly activates the corticospinal tract, providing a peripheral measure of cortical reactivity, such as motor-evoked potentials (MEP), that can be easily recorded. A substantial body of work has indicated that the direction of the TMS-induced current in the brain tissue significantly affects MEP amplitude and latency.<sup>22–24</sup> Specifically, when currents shift from a posterior-to-anterior (PA) to an anterior-to-posterior (AP) direction, with respect to the precentral gyrus, MEP latency increases, likely owing to the recruitment of different neural populations within the stimulated area.<sup>23</sup> Indeed, biophysical modeling has supported the idea that AP currents preferentially activate more rostral regions of M1 than do PA currents.<sup>25</sup> This differential recruitment has proved valuable for investigating the functional role of specific neural circuits during tasks and interventions.<sup>26,27</sup> Notably, the influence of TMS parameters extends beyond the corticospinal output. Several studies have shown that varying the TMS current direction and pulse waveform can modulate cortical plasticity induced by neuromodulatory protocols, as evidenced by behavioral outcomes during motor tasks.<sup>28–31</sup> Indeed, the effects of current direction appear to be modulated by the waveform used to deliver the TMS pulse. Most TMS studies use either monophasic or biphasic pulses.<sup>21,32,33</sup> The electric field induced in the brain follows the rate of change of the magnetic field, with a cosine-shaped waveform generated by a sine-shaped magnetic field. In the case of monophasic stimulation, the magnetic field comprises an initial quarter cycle of a sine wave, producing a single prominent phase of the induced electric field with a dominant direction. In contrast, biphasic pulses comprise a full sine wave cycle, generating a cosine

waveform with three distinct phases. Among these, the second phase, corresponding to the magnetic field's second phase, is the longest and is therefore believed to contribute most strongly to cortical stimulation. Consequently, depending on the pulse features, a specific current orientation may be more effective than the opposite one.<sup>21,34</sup>

Building on this, there is increasing interest in exploring the extent to which stimulation parameters, such as pulse waveform/width or coil orientation—and hence, the direction of the induced currents in the brain—influence cortical responses, including TEPs and derived measures. In recent years, several TMS-EEG studies have addressed this question; however, their findings have never been comprehensively reviewed. Providing a state-of-the-art review on this topic is therefore timely and essential to (1) promote more standardized and interpretable data collection, (2) gain insight into what TEPs truly reflect, and (3) optimize stimulation procedures in relation to the specific objectives of each experiment.

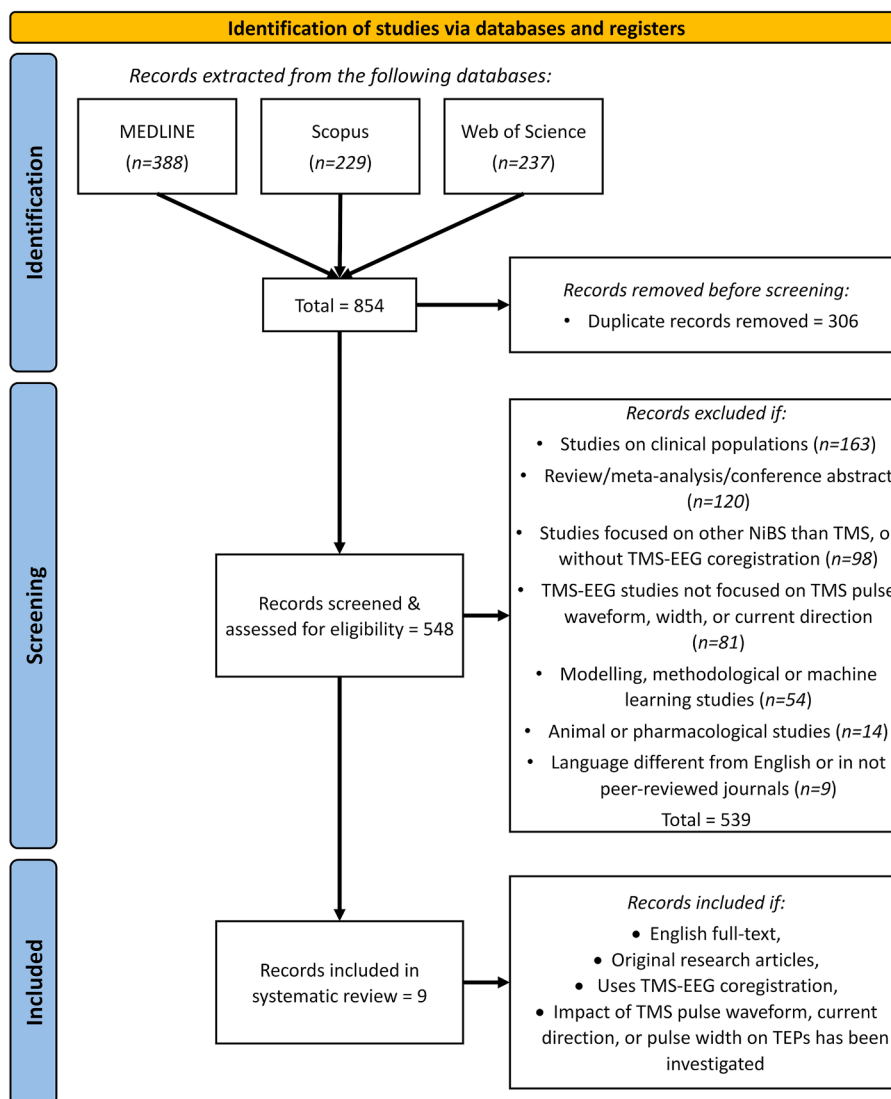
This review aims to systematically describe and critically evaluate findings from TMS-EEG studies that have investigated the impact of the 3 most examined technical parameters in TMS literature (ie, pulse waveform, pulse width, and current direction induced in the brain)<sup>21</sup> on TEPs, providing an up-to-date framework of the current research on this emerging field in addition to methodologic considerations, guidelines, and recommendations for future investigations. In the first part of the review, we synthesize the current evidence on ways TMS parameters influence TEPs. Next, we discuss the broader implications of this body of work, critically evaluating whether the existing evidence truly supports the notion that distinct cortical networks can be selectively engaged through parameter-specific stimulation. Finally, we explore the implications of this assumption and outline directions for future research.

## MATERIALS AND METHODS

We conducted the present systematic review in accordance with the evidence-based criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The process involved the following steps: defining a search strategy, establishing inclusion and exclusion criteria, screening the resulting articles, and extracting and analyzing the data.<sup>35</sup> The PRISMA flowchart is depicted in [Figure 1](#). We registered the present review on the International Prospective Register of Systematic Reviews (PROSPERO)—ID: [CRD420251155960](#).

We conducted a literature search on June 23, 2025, in 3 databases: Web of Science, Scopus, and PubMed (MEDLINE). The Boolean search query was “(TMS) AND (EEG) AND ((pulse waveform) OR (current direction) OR (pulse width) OR (coil orientation) OR (parameters)).” We did not apply any filters for publication location or participant age group during the search. This search yielded 854 articles, which were imported into the Rayyan platform (Cambridge, MA).<sup>36</sup> After removing 306 duplicates, 548 articles remained for screening.

Two researchers (DL, GG) independently assessed articles using Rayyan's software blinding option to minimize bias. Studies were included if they met the following criteria: (1) included healthy participants; (2) systematically manipulated  $\geq$  one TMS parameter in current direction and pulse waveform/width; (3) used single-pulse TMS paradigms; (4) reported EEG analyses assessing how



**Figure 1.** PRISMA flowchart of the literature search and selection process for the present systematic review. NiBS, noninvasive brain stimulation. [Color figure can be viewed at [www.neuromodulationjournal.org](http://www.neuromodulationjournal.org)]

cortical processing changed after manipulation of these TMS parameters; and (5) were peer-reviewed (Fig. 1 presents more information).

After abstract screening, the blinding was removed. Agreement between researchers was 99.5%. Three articles revealed incongruent evaluations among judges, which were discussed and resolved through consensus. After a full-text assessment, the final set of eligible works comprised 9 articles.

For each included study, relevant data were extracted and systematically recorded. The principal information of included studies is reported in Table 1.

## RESULTS

This review included 9 articles that met our inclusion criteria, grouped into two primary sections: studies in which TMS was

applied to M1 ( $n = 5$ ; Fig. 2) and studies targeting areas outside M1 ( $n = 4$ ; Fig. 3). Later, we summarize the primary findings from all these studies.

## STUDIES STIMULATING M1

Historically, the first study to explore the effects of TMS technical parameters on TEPs was conducted by Bonato et al in 2006. Six participants underwent biphasic stimulation of the left M1, with the only parameter manipulated being the current direction induced in the brain (PA vs AP; achieved by orientating the coil at 45° and 135° to the midline, respectively). EEG responses were recorded, and peak morphology up to 300 milliseconds after stimulation was inspected qualitatively. The authors observed that stimulation direction strongly influenced early responses: indeed, components at 20 (N20) and 30 (P30) milliseconds were absent

**Table 1.** List of the Included Articles and Their Primary Methodologic Features

Study	Sample	Stimulation Site	Current Direction	Pulse Waveform	Pulse Width	Stimulation Intensity	ISI Between Pulses	No. of EEG Cap Electrodes	Noise Masking Procedure	TEP Analysis
Bonato et al (2006) <sup>37</sup>	6	Left M1	45°, 135°	Biphasic	~422 $\mu$ S <sup>a</sup>	110% rMT	1 s (no jitter)	19	No	Qualitative evaluation of TEP peaks, whole-scalp level
Casula et al (2018) <sup>19</sup>	19	Left M1	45°, 135°	Monophasic, biphasic	30 $\mu$ S for monophasic and biphasic; 80 $\mu$ S for monophasic PA	90% rMT (computed for each experimental condition)	4-6 s (jittered)	32	Yes	GMFP at 20-50 ms, 50-100 ms, 100-150 ms, 150-250 ms time windows LMFP (C3, FC1, CP1 electrodes) at 20-50 ms, 50-100 ms, 100-150 ms, 150-250 ms time windows amplitude of the first 2 positive and negative TEP peaks (F3, FC1, C3, CP1, P3 electrodes)
Ni et al (2022) <sup>38</sup>	10	Left M1	45°, 135°	Monophasic	84-106 $\mu$ S	80%, 100%, and 120% rMT (computed for each experimental condition)	5.4-6.6 s (jittered)	64	No, ear plugs	TEP peaks (P25, N45, P70, N100, P180, N280; C3, FC1 electrodes + whole scalp cluster-based analysis) amplitude and latency TEPs source estimation GMFP LMFP (C3 electrode) P15 TEP component (F4, FC4 electrodes) amplitude and latency
Guidali et al (2023) <sup>39</sup>	28 (part of the data set of Lucarelli et al)	Left M1	45°, 90°, 135°	Monophasic, biphasic	84-106 $\mu$ S for monophasic and 295-422 $\mu$ S for biphasic <sup>a</sup>	110% rMT (computed for each experimental condition)	4-6 s (jittered)	74	Yes	P15 TEP component (F4, FC4 electrodes) amplitude and latency
Lucarelli et al (2025) <sup>20</sup>	32	Left M1	45°, 90°, 135°	Monophasic, biphasic	84-106 $\mu$ S for monophasic and 295-422 $\mu$ S for biphasic <sup>a</sup>	110% rMT (computed for each experimental condition)	4-6 s (jittered)	74	Yes	TEP peaks (N15, P30, N45, P60, N100, and P180; 4 electrodes for each peak, based on the location of the strongest signal deflection) amplitude and latency

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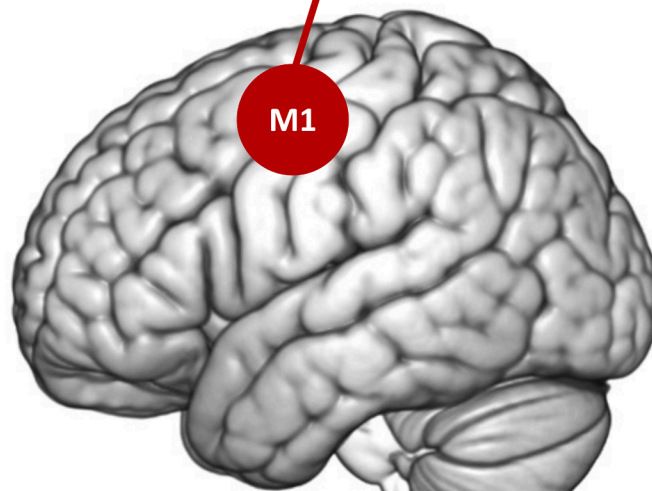
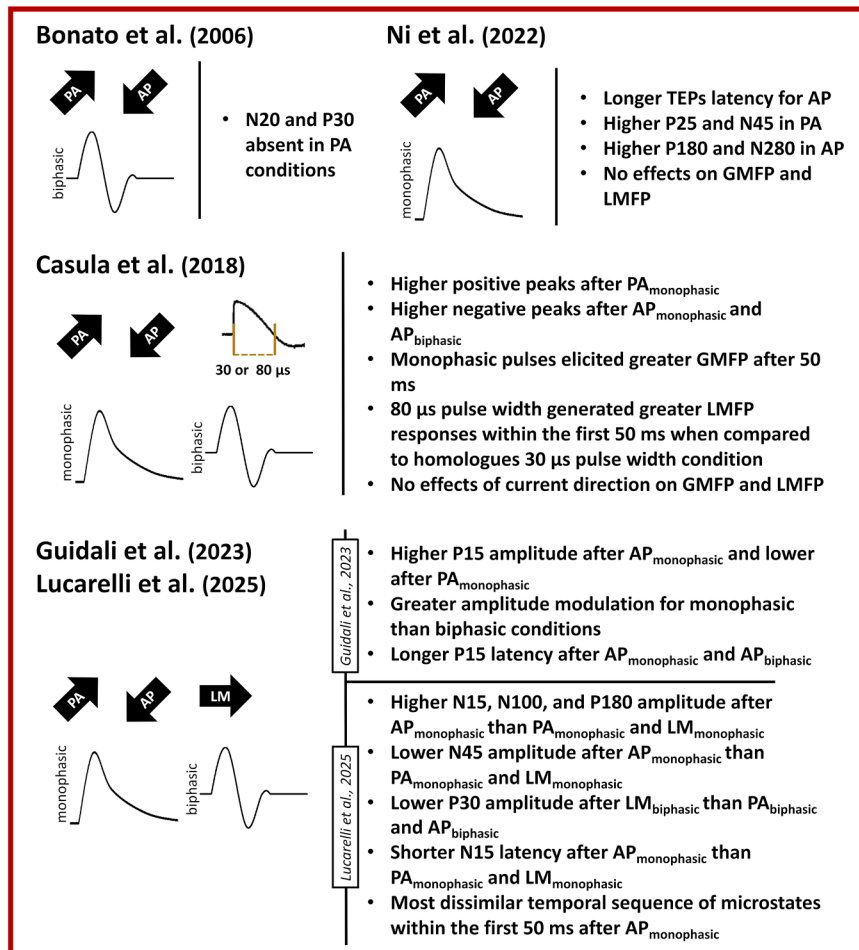
**Table 1.** *Continued*

Study	Sample	Stimulation Site	Current Direction	Pulse Waveform	Pulse Width	Stimulation Intensity	ISI Between Pulses	No. of EEG Cap Electrodes	Noise Masking Procedure	TEP Analysis
Casarotto et al (2010) <sup>43</sup>	10	Left BA19 (occipital) left BA7 (parietal) left BA6 (frontal)	0°, 45°, 90°	Biphasic	280 $\mu$ S	Induced electric field between 110 $\mu$ V–120mV (computed for each experimental condition)	0.7-0.9 s (jittered)	60	Yes	microstates analysis (area under the curve, duration and onset) TEP response amplitude between 0 and 250 ms (whole-scalp)
Casula et al (2022) <sup>40</sup>	17	Right preSMA	0°, 90°, 180°, 270°	Monophasic	80 $\mu$ S	100%, 120%, and 140% rMT	3.6-4.4 s (jittered)	62	Yes	LMFP (Fz, F2, FCz, Fc2) TEP peaks time-frequency analysis (gamma, beta, alpha, theta bands; whole-scalp)
Pieramico et al (2023) <sup>41</sup>	6	Left preSMA	Full Circle 18 orientations in steps of 20°	Monophasic	N/S	TEP amplitude of 5 $\mu$ V–10 $\mu$ V between 15 and 50 ms with mediolateral orientation	2.4-2.7 s (jittered)	64	Yes	Evoked functional connectivity (beta, alpha, theta bands) between the electrode above the stimulation site (FC1) and the electrodes close to the bilateral M1s (FC5, FC3, C5, C3, FC4, FC6, C4, C6)
Granö et al (2025) <sup>42</sup>	6 (same sample of Pieramico et al) <sup>43</sup>	Left preSMA	Full Circle 18 orientations in steps of 20°	Monophasic	N/S	TEP amplitude 5 $\mu$ V–10 $\mu$ V between 15 and 50 ms with mediolateral orientation	2.4-2.7 s (jittered)	64	Yes	TEP response amplitude between 0 and 500 ms (whole-scalp) TEPs source estimation

In the table, current direction degrees are referred to regarding the midline.

TEP, transcranial magnetic stimulation-evoked potential; EEG, electroencephalography; BA, Brodmann area; GMFP, global mean field power; ISI, interstimulus interval; GMFP, global mean field power; LMFP, local mean field power; N/S, not specified; M1, primary motor cortex; preSMA, presupplementary motor area; rMT, resting motor threshold.

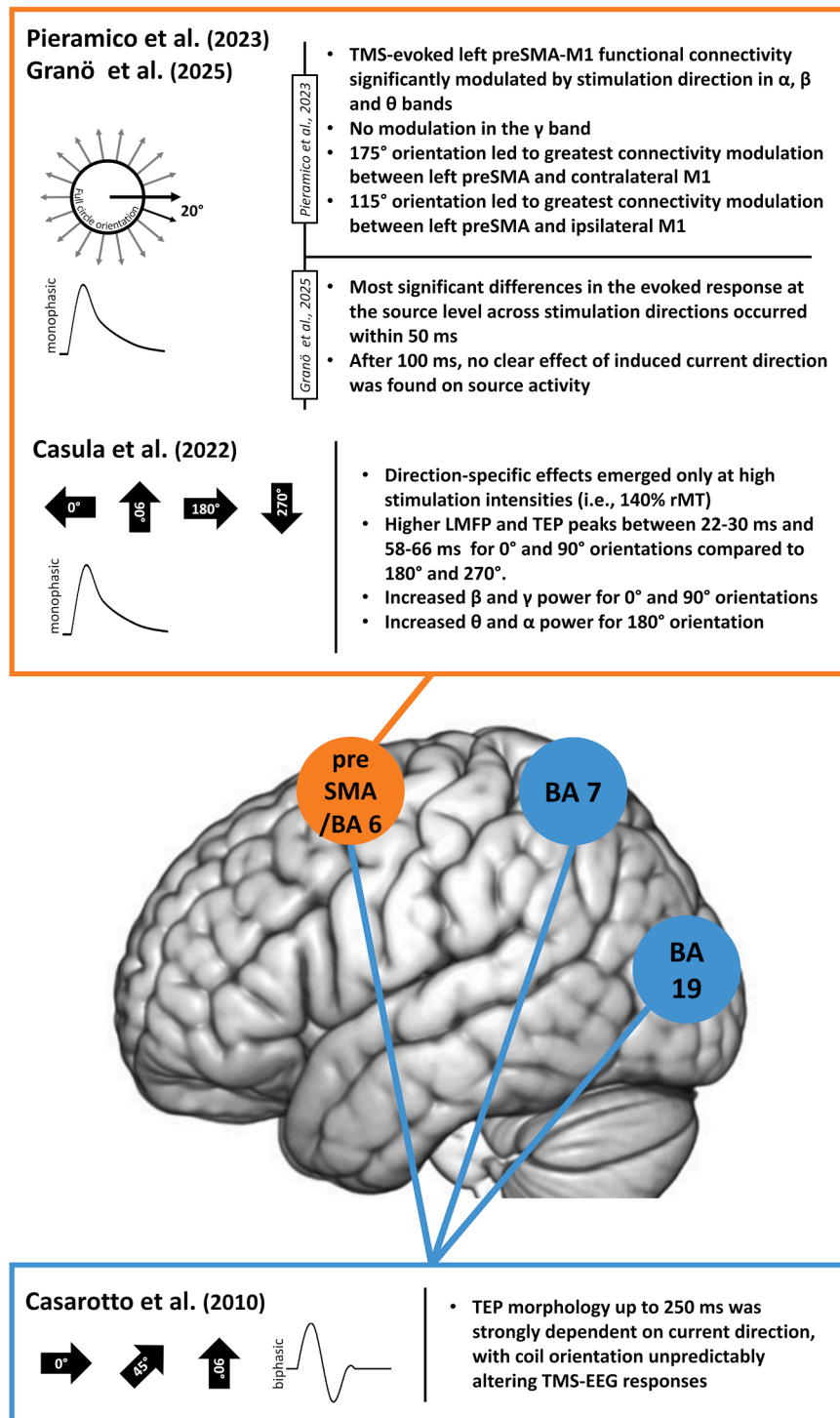
<sup>a</sup>The information was not included in the article of interest; however, it could be retrieved by knowing the TMS model used.



**Figure 2.** Schematic representation of the studies adopting concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) that systematically investigated the impact of TMS technical parameters (ie, pulse waveform/width, direction of the currents induced in the brain) on TMS-evoked potentials (TEP) from the stimulation of the primary motor cortex (M1). For each study, we reported the direction of the induced currents in the brain (arrows and degrees are reported relative to the midline) and the pulse waveforms used, along with their primary results (the main text presents further information). All studies depicted have stimulated the left M1. AP, anterior-to-posterior direction; PA, posterior-to-anterior direction; LM, lateral-to-medial direction; GMFP, global mean field power; LMFP, local mean field power. [Color figure can be viewed at [www.neuromodulationjournal.org](http://www.neuromodulationjournal.org)]

under PA stimulation.<sup>37</sup> Recently, another study focused on manipulating the current direction (PA vs AP) and adopted a more quantitative approach to data analysis.<sup>34</sup> Specifically, Ni et al (2022)

evaluated the current direction effects on TEP amplitude, latency, GMFP, and LMFP in 10 participants, using monophasic pulses at 80%, 100%, and 120% of the individual's rMT. Stimulation was



**Figure 3.** Schematic representation of the studies adopting concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) that systematically investigated the impact of TMS technical parameters (ie, pulse waveform/width, direction of the currents induced in the brain) on TMS-evoked potentials (TEP) from areas other than the primary motor cortex (M1). For each study, we reported the direction of the induced currents in the brain (arrows and degrees are reported relative to the midline) and the pulse waveforms used, along with their primary results (the main text presents further information). All studies except Casula et al. stimulated the left hemisphere. BA, Brodmann's area; preSMA, pre-supplementary motor area; LMFP, local mean field power; rMT, resting motor threshold. [Color figure can be viewed at [www.neuromodulationjournal.org](http://www.neuromodulationjournal.org)]

applied over the left M1, and TEP peaks (P25, N45, P70, N100, N280) were extracted from electrodes underneath the coil. Here, the rMT was computed for both stimulation conditions to ensure

comparability. Across intensities, AP stimulation consistently produced longer TEP latencies than PA stimulation. In contrast to the previous study, early peaks (P25, N45) were bigger with PA

stimulation, whereas later peaks (P180, N280) were significantly higher with AP stimulation. The current direction did not affect GMFP or LMFP. Importantly, source analyses showed that PA stimulation primarily activated M1, whereas AP stimulation also recruited the ipsilateral premotor cortex.<sup>38</sup>

Two studies evaluated not only the role of current direction but also the effects of pulse waveform on M1-TEPs.<sup>20,39</sup> Guidali et al (2023) stimulated the left M1 in 28 healthy participants using PA, AP, and lateromedial (LM; ie, 90° to the midline) orientations with monophasic and biphasic pulses. As Ni et al did, the stimulation intensity (ie, 110% rMT) was adjusted for each stimulation condition. The authors focused solely on an early TEP component, the P15, hypothesized to reflect interhemispheric callosal inhibition. Results showed that P15 amplitude was modulated by current direction only during monophasic stimulation, with monophasic AP currents eliciting the largest response magnitude. Pulse waveform also influenced the P15: monophasic AP stimulation produced a greater component than the homologous biphasic condition, whereas PA and LM showed the opposite pattern, with biphasic waveforms eliciting greater components than monophasic. Latencies were affected by current direction, with AP inducing longer delays than PA and LM for both monophasic and biphasic waveforms.<sup>39</sup> In a subsequent study on the same data set, Lucarelli et al (2025) expanded the analysis to include other well-known M1-TEP components, namely, N15, P30, N45, P60, N100, and P180. In this study, and in contrast to the work of Ni et al (2022), which focused only on electrodes over the stimulation site, TEP peaks were extracted from the cluster of electrodes showing the widest positive or negative deflection within the time window of interest. Results highlighted that biphasic stimulation reduced differences across current directions, consistent with prior findings on the P15, with only the amplitude of P30 recorded during LM stimulation significantly different from that obtained in other stimulation conditions. With monophasic pulses, AP orientation produced greater amplitudes for N15, N100, and P180, but smaller amplitudes for N45, than PA and LM. Latency effects were most pronounced for the earliest component (N15), which, when using a monophasic waveform, showed shorter latency for AP than for PA and LM, opposite to the pattern observed for P15. Furthermore, the authors explored the impact of technical parameters on TMS-induced M1 activity spread with microstate analyses. This investigation revealed that monophasic AP stimulation induced the most divergent temporal sequence of microstate topographies among all orientations, particularly within the first 50 milliseconds after the TMS pulse, suggesting that this combination of TMS parameters maximizes the recruitment of distinct motor circuitries with respect to the other experimental conditions of the study.<sup>20</sup>

Finally, one study explored the effects of TMS pulse width.<sup>19</sup> In this work, Casula et al (2018) manipulated this parameter (30  $\mu$ s vs 80  $\mu$ s) in addition to current direction (PA vs AP), and pulse waveform (monophasic vs biphasic). Nineteen participants received left M1 stimulation, with rMT calculated for each condition. GMFP and LMFP were computed from 20 to 250 milliseconds for 4 post-stimulus windows. TEP peaks were also extracted, and their qualitative inspection revealed reversed topographies between PA and AP stimulation during the earliest time windows, regardless of the waveform used: AP currents elicited greater negativity over the stimulation site and positivity contralaterally, whereas PA currents showed the opposite pattern. Quantitatively, monophasic PA stimulation produced higher positive peaks than did all other

conditions with the same pulse width, whereas monophasic and biphasic AP pulses induced greater negative peaks than PA. Monophasic pulses elicited greater GMFP after 50 milliseconds than did biphasic, and the longer pulse width (ie, 80  $\mu$ s) generated greater LMFP responses within the first 50 milliseconds than did shorter pulse width (ie, 30  $\mu$ s) with the same waveform and orientation features. However, consistent with Ni et al. (2022), no significant effect of current direction was observed in GMFP or LMFP analyses.<sup>19</sup>

### Studies Stimulating Cortical Areas Other Than M1

Casula et al (2022) stimulated the right preSMA in 17 subjects with monophasic pulses at 100%, 120%, and 140% of the individual's rMT, manipulating current direction (0°, 90°, 180°, 270° relative to the midline). LMFP, TEP peaks, and whole-scalp time-frequency analyses were performed. Directional effects emerged at the highest stimulation intensities (ie, 140% of rMT), with the LMFP and TEP peaks between 22 and 30 milliseconds and 58 and 66 milliseconds being larger for 0° and 90° orientations than for 180° and 270°. Time-frequency analyses showed increased beta and gamma power for 0° and 90° orientations, whereas the 180° one enhanced theta and alpha power. These results showed that selecting specific TMS parameters had a critical influence on pre-SMA spatiotemporal dynamics.<sup>40</sup>

Pieramico et al (2023) also targeted preSMA but focused their investigation on TEP-evoked functional connectivity rather than TEP spatiotemporal profile. The authors used multilocus TMS with monophasic pulses in 6 participants, systematically varying pulse orientation in 20° steps (yielding 18 orientations). Evoked functional connectivity between preSMA and bilateral motor clusters was computed in the alpha, beta, and theta bands in the first 500 milliseconds after TMS. Connectivity strength was significantly modulated by stimulation direction across all frequency bands, suggesting that stimulation orientation plays a key role in shaping brain functional interareal communication.<sup>41</sup> The same data set was analyzed by Granö et al (2025). A cluster-based analysis of the evoked responses revealed, in line with M1 studies, that the most significant differences in the evoked responses were observed within 50 milliseconds after stimulation at electrodes close to the TMS. Moreover, source estimation revealed that the direction of the induced electric field has a significant influence on signal propagation. Still, this effect was consistent across subjects only up to 45 milliseconds after the TMS pulse. After 100 milliseconds, the TMS current direction no longer influenced source activity. These results revealed that differences in TEPs effectively reflect distinct signal propagations induced by stimulation current direction within the first 100 milliseconds.<sup>42</sup>

Finally, Casarotto et al (2010) included non-motor areas in their investigation, stimulating a series of left-hemisphere occipital, parietal, and frontal sites, corresponding to Brodmann areas 19, 17, and 6, respectively. The authors used biphasic pulses with the coil orientated at 0°, 45°, and 90° (relative to the midline). TEPs were analyzed up to 250 milliseconds after stimulation, and a divergence index was operationalized to quantify orientation effects. Their results indicated that TEP morphology was strongly dependent on current direction, with coil orientation unpredictably altering TMS-EEG responses. This evidence suggests that TEPs reflect deterministic properties of the stimulated neuronal circuit, and when areas outside the motor system are targeted.<sup>43</sup>

## DISCUSSION

Overall, the reviewed literature indicates that variations in TMS parameters substantially influence TEP morphologies and spatiotemporal characteristics, likely reflecting differences in the cortical population activated by the TMS pulse. The most replicated finding concerns the role of current direction in shaping cortical responses to TMS, with evidence suggesting that this effect is further modulated by the pulse waveform. Specifically, studies have shown that during monophasic stimulation of M1, TEP amplitudes vary as a function of current direction.<sup>20,38,39</sup> Regarding TEP latencies, modulation has primarily been observed in the earliest components (N15 and P15). Evidence regarding the latency of later peaks is less consistent: Lucarelli et al (2025) reported no significant differences, whereas Ni et al (2022) observed longer latencies across all components (P25, N45, P70, N100, and P280) with AP stimulation than with PA. The interaction between pulse waveform and current direction likely reflects the intrinsic biophysical properties of the stimulation, whereby monophasic pulses predominantly induce current flow in a single direction, whereas biphasic pulses, comprising two successive phases, induce two physiologically effective but oppositely directed currents.<sup>21,44,45</sup> Consequently, monophasic pulses may provide greater direction-specificity than do biphasic pulses.<sup>34</sup> However, systematic investigation of waveform effects beyond M1 is lacking. For example, studies targeting the preSMA have not systematically manipulated pulse waveform within the same experiments and have predominantly used monophasic pulses.<sup>40–42</sup> Casarotto et al (2010) also investigated the preSMA, but exclusively using biphasic pulses, and further evaluated other cortical regions using the same waveform.<sup>43</sup> This limits conclusions about the extent to which the direction-specificity observed in M1 generalizes to other areas. In this vein, it is worth noting that hints about the possible contribution of pulse waveform to TEPs recorded from regions outside M1 come from a not peer-reviewed preprint (hence not considered in the present systematic review) by Pisoni et al (2018). They stimulated a premotor area roughly corresponding to the preSMA and found that biphasic pulses evoked larger early TEP components than do monophasic pulses that, conversely, elicited a greater N100 when orientated perpendicularly to the stimulated gyrus.<sup>46</sup>

Regardless of pulse waveform, the effect of current direction is most pronounced in the earliest TEP components, likely reflecting the direct activation of the stimulated region.<sup>47</sup> Casula et al (2018) reported distinct and opposite topographical patterns when switching from PA to AP M1 stimulation, with AP eliciting both increased negative and positive early components.<sup>19</sup> Similarly, the amplitudes of M1-N15 and M1-P15 were consistently larger with AP stimulation.<sup>20,39</sup> These findings indicate that the earliest M1 cortical responses (within the first 20 milliseconds after the stimulation) are wider under AP-directed stimulation. Although modulation of TEP amplitude alone is insufficient to infer the recruitment of different neuronal populations, given that amplitude also may reflect differences in stimulation efficacy, modulation of TEP latencies (M1-N15 and M1-P15) provides more compelling evidence for the recruitment of distinct neural circuits.<sup>20,23</sup> Indeed, different neuronal populations exhibit distinct activation delays due to the time required to generate action potentials, whether mediated by monosynaptic or transsynaptic pathways, causing measurable latency shifts in TEP components.<sup>23</sup> Moreover, microstates and source analyses directly support the engagement of separate neural networks depending on

stimulation direction. Microstate analysis on M1 TEPs revealed that early microstates evoked by (monophasic) AP stimulation differed substantially from those elicited by LM and PA directions,<sup>20</sup> whereas source analysis of M1 stimulation showed that AP pulses recruited more anterior regions, including premotor cortex, than PA.<sup>38</sup> Similar direction-dependent differences in propagation have been observed after preSMA stimulation up to 45 milliseconds after stimulation, with consistent results across participants.<sup>42</sup> These findings corroborate evidence from MEP and modeling studies, indicating that varying current direction while keeping the stimulation site constant recruits distinct neuronal populations.<sup>23,25</sup> More specifically, AP stimulation is believed to preferentially recruit more superficial and rostral neurones in M1, primarily interneurons involved in corticocortical communication. In contrast, PA stimulation predominantly activates superficial neurones associated with the corticospinal tract.<sup>23,48–50</sup> Therefore, AP current direction may be more suitable for targeting corticocortical networks than PA.

Later TEP components also show direction-dependent modulation; however, these effects are weaker and less consistent across studies. For example, M1-N45 amplitudes were reported to be larger with PA and LM stimulation than with AP stimulation, whereas M1-P25/P30 showed the opposite pattern.<sup>20,38</sup> Casula et al (2018) observed an enhancement of positive peaks with PA stimulation and a decrease in negative peaks with AP over M1, although these findings have not been consistently replicated.<sup>19</sup> Interestingly, after preSMA stimulation, source-level analyses revealed no direction-dependent differences beyond 100 milliseconds,<sup>42</sup> in line with microstate findings from M1 stimulation.<sup>20</sup> However, M1-TEP peaks after 100 milliseconds tended to be larger under AP stimulation.<sup>20,38</sup> Altogether, these findings suggest that neural activity occurring from approximately 100 milliseconds after the TMS pulse may no longer be influenced by the spatial specificity induced by the stimulation parameters, as reflected by the absence of topographical dissimilarity. Instead, the differences observed in TEPs may reflect variations in the effectiveness of recruiting the cortical circuits responsible for N100 generation. Indeed, evoked activity approximately 100 milliseconds after stimulation is believed to be driven primarily by recurrent network feedback rather than by local activity at the stimulation site,<sup>51</sup> consistent with evidence showing that N100 amplitude does not differ across stimulation of distinct cortical areas.<sup>52</sup> However, these interpretations should be made with caution because late TEP components are often influenced by secondary processing related to TMS-induced auditory and somatosensory artifacts, rather than exclusively reflecting the genuine neural response of the targeted region.<sup>53,54</sup> For instance, accounting for the auditory processing of the TMS pulse (ie, the “click” that the coil produces every time a pulse is delivered, which volume positively correlates with the stimulation intensity) is critical in this context, considering that recalculating rMT for each stimulation condition likely produces different noise levels across blocks. Such variability may disproportionately affect later TEP components, especially given that AP stimulation typically requires higher intensities than PA stimulation.<sup>39,55,56</sup> Notably, only one study<sup>20</sup> explicitly included stimulation intensity as a covariate to control for this confound, highlighting that TMS intensity largely accounted for the observed effects on the M1-P180 and corroborating the notion that modulations found for late TEP components should be interpreted with caution.

Beyond conventional peak-based analyses, alternative measures such as GMFP and LMFP also have been applied. These measures have

generally not revealed robust current-direction effects, at least for M1 stimulation,<sup>19,38</sup> in contrast to pulse waveform and pulse width that indeed affect them.<sup>40</sup> One possible explanation is that GMFP and LMFP may lack sufficient sensitivity to detect subtle direction-specific effects because they primarily reflect the overall balance of excitatory and inhibitory activity.<sup>57</sup> However, these measures may be more responsive to stimulation parameters that modulate the energy characteristics of the pulse, including its waveform and width.

Frequency-domain analyses provided additional evidence of direction-specific effects, particularly for preSMA stimulation. Alterations were observed in theta, alpha, beta, and gamma power,<sup>40</sup> in addition to connectivity changes in theta, alpha, and beta bands between the stimulated region and motor areas.<sup>41</sup> These findings corroborate the hypothesis that distinct neuronal groups are recruited depending on stimulation direction, consistent with the notion that neuronal populations exhibit characteristic resonance frequencies.<sup>58</sup> Furthermore, in line with the communication-through-coherence framework,<sup>59,60</sup> direction-dependent connectivity changes may reflect recruitment of neuronal groups that synchronize within specific frequency bands, and hence, it could be hypothesized that variations in TMS parameters can affect the whole-brain communication profile of the targeted area. A first step in this direction was taken in a recent study by our research group targeting M1, not yet published at the time the present systematic review was conducted.<sup>61</sup> Here, using the same data set of,<sup>20,39</sup> we explored whether and how whole-brain TMS-induced functional connectivity in the alpha and beta bands changes according to the different TMS parameters exploited. Results showed that monophasic pulses led to stronger induced connectivity than biphasic ones in the alpha band, with AP currents inducing the most significant and widespread modulation. Under biphasic stimulation, AP elicited the most substantial connectivity changes in the alpha band and the weakest in the beta band, whereas biphasic PA showed the opposite pattern. These findings have important implications for future studies exploiting TMS-EEG-derived functional connectivity indexes, suggesting that TMS parameters can significantly modulate the motor system's oscillatory dynamics, recruiting distinct functional networks related to the stimulated M1.<sup>61</sup>

Taken together, TEP findings align with evidence from MEP and biophysical modeling studies,<sup>23,25</sup> pointing to the possibility of engaging distinct neuronal populations through selective modulation of TMS parameters. This specificity applies not only to corticospinal but also to corticocortical pathways, within and outside M1. Although most studies have focused on spatiotemporal aspects,<sup>19,20,37–39,43</sup> some evidence also points to modulation in the frequency domain and connectivity patterns.<sup>40–42</sup>

Nevertheless, the investigations conducted to date on this topic present limitations that future studies must consider. First, the cited studies had relatively small sample sizes (Table 1), which undermines the generalizability of their findings to the broader population. Furthermore, as noted earlier, the TMS-EEG literature is characterized by methodologic heterogeneity at multiple stages of data collection and analysis,<sup>3,15,16</sup> which hinders direct comparison with the studies reviewed here. For instance, during data collection, noise-masking procedures to mask the TMS click varied widely: Bonato et al (2006) used none, whereas Ni et al (2022) used only earplugs without white noise. Another major source of variability was whether stimulation intensity was calibrated for each

set of parameters adopted in a given experimental condition. Several studies recomputed the rMT and set TMS intensity accordingly,<sup>19,20,38,39,43</sup> whereas others did not.<sup>37,40–42</sup> Recomputing the rMT when M1 is targeted, or more generally, determining the optimal stimulation intensity for each condition, is highly informative, given that stimulation parameters strongly influence the TMS intensity needed to elicit neuronal activation efficiently.<sup>55</sup> At the analysis stage, in addition to variability in preprocessing steps across studies, some works restricted measurements to electrodes beneath the coil.<sup>19,37</sup> In contrast, others adjusted the region of interest on the basis of the location of maximal signal deflection,<sup>20,38,39</sup> thereby also capturing propagation effects. Last but not least, as already highlighted, investigations have been primarily restricted to the motor system (M1 and preSMA), with limited exploration of other brain regions that play vital roles in brain functioning and are known to be elective sites of TMS, especially in clinical settings (eg, dorsolateral prefrontal cortex, inferior parietal lobule).<sup>62</sup>

Given the methodologic heterogeneity across the limited number of available studies and the partial overlap among data sets (Table 1), we believe these findings should warrant further investigation to confirm the framework proposed in the present review. Nevertheless, these results, although still preliminary, have substantial implications for future TMS studies. They underscore that overlooking the impact of key TMS parameters, such as the optimal pulse waveform or coil orientation for a given cortical area, may critically determine the neural population engaged by the pulse, both within the target site and across its interconnected regions, in turn, affecting stimulation's aftereffects and their reproducibility. Building on the evidence reviewed here, future studies should capitalize on parameter-dependent effects to investigate ways their systematic modulation could affect large-scale network communication and related functional outcomes,<sup>63,64</sup> ultimately informing the optimal combination of parameters given a specific experimental aim. Significantly, recognizing that exact sets of TMS parameters are better suited to recruit a particular corticocortical circuit within the same targeted region could substantially improve the design of neuromodulatory protocols aimed at corticocortical pathways or related networks—such as paired associative stimulation<sup>65,66</sup>—and enhance the assessment of their plastic aftereffects. In this vein, another future line of research could be to extend the use of TEPs and related TMS-EEG indexes to investigate the impact of parameters used during neuromodulatory protocols, thereby improving the effectiveness of these TMS paradigms and reducing their interindividual variability. For instance, a recent study showed that 1-Hz repetitive TMS over M1 with biphasic (PA-)AP pulses elicited greater pre- vs postmodulation of M1-TEP components than did the reversed (AP-)PA direction, suggesting greater cortical effectiveness with this combination of technical parameters.<sup>67</sup> Finally, extending this investigation beyond the motor system will be essential in the coming years, and “next-generation” TMS stimulators, such as programmable<sup>68–70</sup> or multilocus TMS,<sup>71,72</sup> represent up-and-coming tools. At the same time, advances in TMS-EEG methods, as with the feasibility of assessing genuine TEP components already in the first 2 to 3 milliseconds after the pulse,<sup>73–75</sup> will allow extending this investigation to components likely reflecting direct cortical responses to TMS (ie, immediate TEPs), which potentially tend to be more influenced by the induced electric field's

parameters. For instance, Beck et al (2024) showed that immediate TEPs elicited with biphasic AP direction over M1 had a smaller amplitude than those elicited with the reversed direction, mimicking the pattern usually observed for MEP amplitude and suggesting that these components can be functional for tracking the direct activation of the stimulated area.<sup>73</sup>

## CONCLUSION

In conclusion, the literature reviewed here, although preliminary and primarily based on studies that stimulate the motor system, highlights that TMS technical parameters could strongly influence TEPs and derived indexes, in turn affecting the variability typically observed in TMS-EEG studies. Hence, in line with the most recent recommendations on the use of this combined technique,<sup>6</sup> we warrant that future TMS-EEG studies report the exact technical parameters used during TEP recording (ie, pulse waveform/width, induced current direction, in addition to coil orientation), thereby improving not only the reproducibility of results but also the explanation of divergent findings from previous literature targeting, for example, the same area or cortical network. In this framework, approaches based on subject-specific coil positioning adjustments to minimize, for instance, TMS-related muscular artifacts, should be carefully used and meticulously described, given the potential variability introduced when signals obtained from different subjects and with distinct coil orientations are collapsed. The reviewed literature also provides valuable guidelines for selecting TMS parameters based on the specific experimental aim. The available evidence suggests that monophasic stimulation is a more sensitive and controllable approach for isolating the effects of TMS parameters on EEG outcomes and should therefore be preferred in future studies aiming to systematically investigate and optimize TMS administration, for example, for developing TEP-based biomarkers. However, this recommendation may not extend to clinical applications, in which broader recruitment of neuronal populations, often achieved with biphasic stimulation, could be advantageous for maximizing the therapeutic effects of TMS-based neuromodulatory protocols, especially when targeting a lesioned brain.

## Authorship Statements

Delia Lucarelli was responsible for study conceptualization, methods, investigation, formal analysis, data curation, visualization, and writing—original draft. Vittorio Pizzella and Laura Marzetti were responsible for funding acquisition, supervision, writing—review and editing. Giacomo Guidali was responsible for study conceptualization, methods, investigation, validation, data curation, visualization, supervision, and writing—original draft. All authors approved the final version of the manuscript.

## Conflict of Interest

The authors reported no conflict of interest

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## COMMENT

TMS-EEG provides a unique opportunity to causally probe the brain’s neurophysiologic properties, including cortical excitability and connectivity, thereby positioning it as a powerful platform for developing biomarkers of treatment response and advancing mechanistic understanding of both psychiatric disorders and their interventions. The study by Lucarelli et al highlights an important aspect of stimulation parameters and underscores the need for detailed reporting of these characteristics to facilitate standardization, reproducibility, and cross-study comparability.

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