Neuroscience and Biobehavioral Reviews 155 (2023) 105434

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Somatosensory input in the context of transcranial magnetic stimulation coupled with electroencephalography: An evidence-based overview

M. Mancuso [a], A. Cruciani [b,c], V. Sveva [d], E.P. Casula [e], K. Brown [f], J.C. Rothwell [g], V. Di Lazzaro [b,c], G. Koch [h], L. Rocchi [i,*]

[a] Department of Human Neurosciences, University of Rome "Sapienza", Viale dell'Università 30, 00185 Rome, Italy
[b] Department of Medicine and Surgery, Unit of Neurology, Neurophysiology, Neurobiology, and Psychiatry, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo, 21, 00128 Rome, Italy
[c] Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, 00128 Rome, Italy
[d] Department of Anatomical and Histological Sciences, Legal Medicine and Orthopedics, University of Rome "Sapienza", Piazzale Aldo Moro, 5, 00185 Rome, Italy
[e] Department of System Medicine, "Tor Vergata" University of Rome, Via Montpellier 1, 00133 Rome, Italy
[f] Department of Kinesiology, University of Waterloo, 200 University Ave W, N2L 3G5 Waterloo, ON, Canada
[g] Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, WC1N 3BG London, United Kingdom
[h] Non-Invasive Brain Stimulation Unit, IRCCS Santa Lucia Foundation, Via Ardeatina, 306/354, 00179 Rome, Italy
[i] Department of Medical Sciences and Public Health, University of Cagliari, Cittadella Universitaria di Monserrato Blocco I S.S, 554 bivio per Sestu 09042, Monserrato, Cagliari, Italy

ARTICLE INFO

Keywords:
Transcranial magnetic stimulation
Electroencephalography
TMS-EEG
Somatosensory stimulation
Evoked potentials
Cranial nerves
Trigeminal nerve
Facial nerve

ABSTRACT

The transcranial evoked potential (TEP) is a powerful technique to investigate brain dynamics, but some methodological issues limit its interpretation. A possible contamination of the TEP by electroencephalographic (EEG) responses evoked by the somatosensory input generated by transcranial magnetic stimulation (TMS) has been postulated; nonetheless, a characterization of these responses is lacking. The aim of this work was to review current evidence about possible somatosensory evoked potentials (SEP) induced by sources of somatosensory input in the craniofacial region. Among these, only contraction of craniofacial muscle and stimulation of free cutaneous nerve endings may be able to induce EEG responses, but direct evidence is lacking due to experimental difficulties in isolating these inputs. Notably, EEG evoked activity in this context is represented by a N100/P200 complex, reflecting a saliency-related multimodal response, rather than specific activation of the primary somatosensory cortex. Strategies to minimize or remove these responses by EEG processing still yield uncertain results; therefore, data inspection is of paramount importance to judge a possible contamination of the TEP by multimodal potentials caused by somatosensory input.

1. The problem of sensory input in the context of TMS-EEG

Interest in transcranial magnetic stimulation coupled with electroencephalography (TMS-EEG) has been growing considerably in recent years. This technique allows the study of brain activity by recording TMS-evoked potentials (TEPs, Fig. 1) (Hernandez-Pavon et al., 2023) and oscillations (Biondi et al., 2022) elicited by TMS. Thanks to the high temporal resolution of EEG, TMS-EEG allows the assessment of fundamental neurophysiological parameters such as cortical excitability (Ilmoniemi et al., 1997; Massimini et al., 2005; Paus et al., 2001), connectivity (Casula et al., 2020; Casula et al., 2021) and plasticity (Ferreri and Rossini, 2013; Rocchi et al., 2018), giving a unique opportunity to study human brain networks in vivo. In addition, TMS-EEG is being extensively used to assess the pathophysiology of many disorders of the central nervous system, including stroke (Hordacre et al., 2019; Keser et al., 2022; Sarasso et al., 2020), dementia (Casula et al., 2022b; Nardone et al., 2021), epilepsy (Tsuboyama et al., 2020), disorders of consciousness (Napolitani et al., 2014) and neuropsychiatric diseases (Cao et al., 2021; Ferrarelli and Phillips, 2021).

Despite the many research applications of this technique, the interpretation of TMS-EEG signals can be made difficult by the auditory and somatosensory activation generated by TMS. The first is caused by the TMS click, which can activate the auditory system via air- or bone conducted sound (Nikouline et al., 1999; ter Braack et al., 2015). This

* Corresponding author.
E-mail address: l.rocchi@ucl.ac.uk (L. Rocchi).

https://doi.org/10.1016/j.neubiorev.2023.105434
Received 18 June 2023; Received in revised form 11 October 2023; Accepted 22 October 2023
Available online 26 October 2023

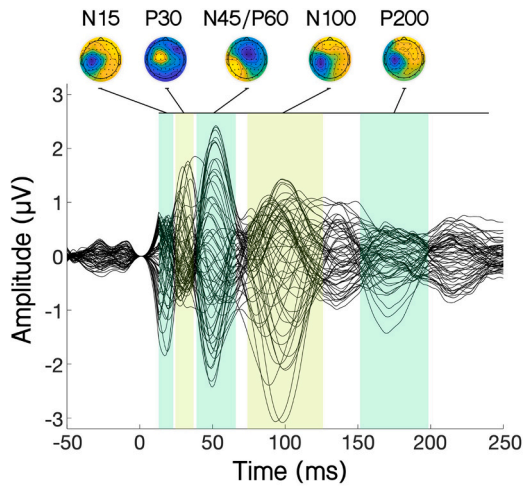

Fig. 1. Butterfly plot of typical TEP from left M1 stimulation at 90 % resting motor threshold, recorded with 64 passive electrodes. Topographies of main peaks (N15, P30, N45/P60, N100 and P200) are provided. Signals represent the average of fifteen healthy subjects. As the TMS click was suppressed, no vertex N100/P200 is visible.

process results in a well-characterised sequence of auditory evoked responses (AEPs), the largest represented by a vertex negativity occurring around 100 ms, followed by a positive wave with similar distribution, peaking around 200 ms (Cristofari et al., 2023; Nikouline et al., 1999; Rocchi et al., 2021). Although AEPs can theoretically contaminate TEPs, effective strategies exist to minimize or abolish them, including the use of masking noise (Massimini et al., 2005; Russo et al., 2022) ear defenders (Rocchi et al., 2021) and a layer of sponge underneath the coil (Leodori et al., 2022a; Massimini et al., 2005; Rocchi et al., 2021; Russo et al., 2022). Importantly, it has been demonstrated that, by the application of one or more of these procedures, it is possible to completely suppress AEPs in some experimental conditions (Leodori et al., 2022a; Massimini et al., 2005; Rocchi et al., 2021; Russo et al., 2022). In addition to auditory stimulation (AS), TMS can theoretically induce activation of somatosensory pathways by at least five different mechanisms (Fig. 2): 1) contraction of craniofacial muscle, 2) activation of somatosensory nerve trunks, 3) stimulation of free cutaneous nerve endings, 4) coil vibration, 5) activation of pain receptors. However, unlike AEPs, the impact of possible somatosensory evoked potentials (SEPs) on TEPs has not been well characterized. This is due to two main reasons: first, it is not clear whether TMS can actually activate somatosensory pathways according to all the mechanisms above. Additionally, even if these forms of activation took place, the features of resulting SEPs, or even their occurrence, are not necessarily predictable. The scope of the present review stemmed from these two gaps in knowledge. We first aimed to provide an overview of the available evidence about the mechanisms through which TMS may induce somatosensory stimulation in the craniofacial district; secondly, we reviewed current knowledge about the possibility that these forms of activation could elicit a SEP. Lastly, we put the findings in the context of TMS-EEG studies, in particular those which aimed to investigate a possible contamination of TEPs by SEPs (Conde et al., 2019; Gordon et al., 2018; Gordon et al., 2021; Rocchi et al., 2021).

2. Methods

A comprehensive literature search on different databases (PubMed/MEDLINE, Scopus, Google scholar and simple Google search) was conducted independently by three researchers (M.M., A.C., V.S.). Only publications in English, French or Italian were selected. For Sections 3.1–3.5, the search strategy was designed to gather information on experimental evidence and physiological plausibility of somatosensory activation in the craniofacial district (contraction of craniofacial muscle, activation of somatosensory nerve trunks, stimulation of free cutaneous nerve endings, coil vibration, activation of pain receptors) by TMS and electrical stimulation (ES), and about possible associated EEG responses. For Section 3.6, only TMS-EEG articles specifically addressing the issue of somatosensory input by TMS and/or ES were considered. The reference list of each selected article was checked to screen for additional studies possibly worth including, but not captured by the original search method. Results were framed into a narrative overview. A formal risk of bias assessment was not conducted; instead, potential biases in individual studies were considered during synthesis and interpretation of the overall results.

3. Different types of somatosensory inputs in the craniofacial district and possible associated EEG responses

3.1. Contraction of craniofacial muscles

Contraction of cranial muscles can easily occur during TMS, being more frequent with higher stimulation intensities and when lateral cortical areas are stimulated (Mutanen et al., 2013); this is because cranial muscles are distributed in lateral aspects of the head, whereas no muscle fibres are located close to the vertex (Westbrook et al., 2022). Cranial muscles commonly activated by TMS include the frontalis, orbicularis oculi, temporalis, and masseter. Contraction of these muscles can occur by two different mechanisms: 1) direct activation of muscle fibres close to the stimulation site by TMS pulse; 2) activation of low threshold intramuscular motor nerve endings (Troni et al., 1983). While

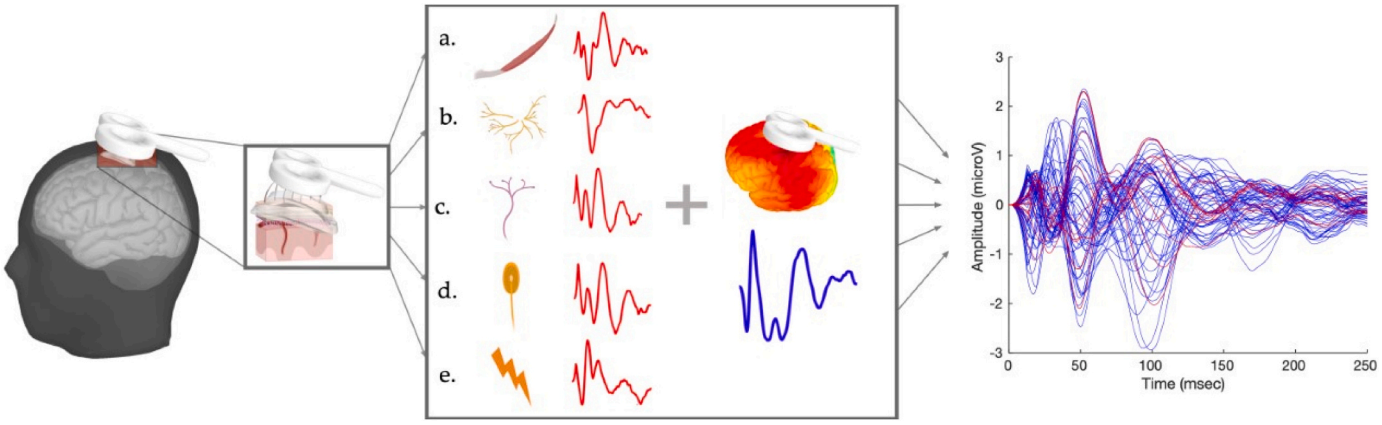

Fig. 2. Possible sources of somatosensory activation during TMS-EEG recording. A: contraction of craniofacial muscle; b: activation of somatosensory nerve trunks; c: stimulation of free cutaneous nerve endings; d: coil vibration; e: activation of pain receptors. The figure has been created with BioRender.com.

the former is unlikely due to the high threshold of muscle fibres, the latter may occur when TMS is applied on scalp areas far from the vertex, where the mentioned muscles lie (Rogasch et al., 2014). On the other hand, a TMS pulse may depolarize motor axons within a cranial nerve trunk along its pathway, generating a compound muscle action potential (CMAP) in muscles innervated by that nerve (Groppa et al., 2012). In this case, CMAPs may be generated in muscles not necessarily close to the stimulation site. In the craniofacial district, this may occur for facial and trigeminal nerve stimulation.

CMAPs generated by cranial nerves stimulation have been mostly studied in the clinical setting, to assess integrity of nerve trunks. The facial nerve provides somatic innervation to facial muscles (Dulak and Naqvi, 2021), and, for example, non-invasive stimulation of its intracranial pathway has been studied as a potential tool for evaluation and prognosis of facial nerve palsy (Cocito et al., 2003; Seki et al., 1990). Previous work has demonstrated the possibility to obtain reliable CMAPs from facial muscles when TMS is applied on the ipsilateral hemisphere with a round coil (Benecke et al., 1988; Maccabee et al., 1988; Schriefer et al., 1988). This effect is dependent on coil positioning: CMAPs are more easily obtained with stimulation over temporal areas, while no muscle responses may be obtained by application of TMS over central regions (Seki et al., 1990). It is to note that, in the research setting, the use of round coils has been largely replaced by figure of eight coils, which allow for a more focal stimulation by producing maximal current at the intersection of two round components (Hallett, 2007). The latter coils have been used as well to elicit CMAPs by facial nerve stimulation, but with less efficacy. Tokimura and colleagues, for instance, were able to record CMAPs only when a figure of eight coil was placed over the stylomastoid foramen, the emergence point of the facial nerve, and with an anterior-posterior current direction (+30 to −30 degrees on the transverse plane (Tokimura et al., 1993). Another study stimulated the nerve at 68 % MSO from the scalp surface, at a location 6–10 cm lateral to the vertex, and 1–2 cm off the mid-auricular line (Dubach et al., 2004). Important information about the role of coil location were obtained in further studies, which suggested that CMAPs from facial-innervated muscles cannot be obtained if a figure of eight coil is placed closer than 4–6 cm from the vertex (Rödel et al., 1999) or when stimulating the hand motor cortex with a subthreshold intensity (Rocchi et al., 2021).

The motor component of the trigeminal nerve, which provides innervation to masticatory and other muscles (the mylohyoid, anterior belly of the digastric, tensor veli palatini, and tensor tympani muscles) (Huff and Daly, 2021), is another potential target for TMS, albeit less accessible than the facial nerve. Responses from trigeminal-innervated muscles have been observed when TMS was applied with a round coil and high stimulation intensities over lateral areas of the scalp (Macaluso et al., 1990; Schmid et al., 1992, 1995), at least 4 cm from the vertex (Benecke et al., 1988). There is only limited information on the possibility of trigeminal activation with a figure of eight coil, as only one study was performed and did not find any response from the masseter muscle with subthreshold stimulation of the hand motor cortex (Rocchi et al., 2021).

Overall, the information available in the literature points towards the possibility of inducing craniofacial muscle activation during TMS, both due to local effects and to stimulation of motor nerve trunks, the latter in at least some experimental contexts. It is conceivable that muscle contraction itself leads to activation of receptors from muscle and possibly from tendons, joints and overlying skin, with generation of afferent somatosensory volleys; but is this activity sufficient to generate a measurable EEG signal? We found that unequivocal evidence in this regard is lacking, as EEG was not recorded in the mentioned studies. Additionally, activation of cranial nerves by TMS is likely not specific for motor axons. Depolarization of mixed nerves, with simultaneous activation of somatosensory fibres, would more likely occur; this would lead to generation of somatosensory action potential which could confound any possible EEG activity due to muscle contraction only. To understand whether the latter is able to generate SEP, an experimental method for obtaining muscle contraction without activation of somatosensory axons should be devised. Two possible solutions are intramuscular electrostimulation (IMES) or passive movement (PM). IMES of the abductor pollicis brevis muscle and PM of the fingers have been demonstrated to elicit measurable EEG response (Mima et al., 1996; Niddam et al., 2005; Seiss et al., 2002). However, no data exist on IMES or PM of craniofacial muscles. Therefore, whether contraction of the latter is able, per se, to generate EEG signals, is an open question. Due to the paucity of receptor structures, such as spindles, in facial muscle (Cobo et al., 2017; Welter et al., 2022), it is conceivable that EEG responses possibly generated by their contraction would be smaller compared to distal muscles.

3.2. Direct activation of somatosensory nerve trunks

In principle, TMS may activate somatosensory nerve trunks close to the stimulation site. For instance, this might be the case for pure somatosensory nerves in the posterior (e.g., greater occipital, lesser occipital, great auricular, etc.) or the anterior (sensory branches of the trigeminal nerve) aspect of the head. Literature on activation of posterior nerves is scant, as only the greater occipital nerve, which originates from the second and third cervical nerves (Hogan and Abram, 1997), has been used as target for ES; no sensory nerve action potentials have been reliably recorded (Sand and Becser, 1998) and EEG recording has not been performed in this context.

More studies have investigated the possibility of obtaining SEPs by stimulating branches of the trigeminal nerve. Stimulation was either performed on purely sensory nerves, or mixed nerves, while checking for possible CMAPs. In most studies, a cortical W-shaped response, predominantly contralateral, could be obtained, with responses which were highly variable in terms of latency (Arcuri et al., 2006; Badr et al., 1983; Bennett and Jannetta, 1980; Fagade and Wastell, 1990; Troni, 2022) and, in general, at a faster frequency than TEPs (around 50 Hz). Stimulation intensities were also variable, ranging from light tickling (Badr et al., 1983) to pain (Fagade and Wastell, 1990). One study deserves particular attention, since the authors stimulated the supraorbital nerve, with the aim of mimicking its possible activation during TMS of the prefrontal cortex; bilateral evoked responses were found in centro-parietal electrodes, the largest represented by a negative peak at around 140 ms (Pokorny et al., 2022), much later that the N100 component often described in TEPs from M1 (Mancuso et al., 2021; Rawji et al., 2021) and also not recognizable in TEPs obtained by stimulation of the dorsolateral prefrontal cortex (Desforges et al., 2022; Zrenner et al., 2020) or other cortical areas (Cruciani et al., 2023).

Overall, current evidence points to clear differences between TEPs and SEPs obtained by cranial nerve stimulation. It is also not clear whether the latter would take place in the TMS context. In this regard, it is worth noticing that, with ES of trigeminal sensory branches, evoked responses may be lost in case of small displacements of the stimulating electrodes (Badr et al., 1983); it is thus possible that even small changes in position of the TMS coil occurring during stimulation may contribute to suppress possible SEPs.

3.3. Stimulation of free cutaneous nerve endings

Stimulation of free cutaneous somatosensory nerve endings (mostly Aβ) in the scalp invariably occurs during TMS, due to the electrical field induced in the skin, and contributes to the tapping sensation associated with coil firing (Deflorio et al., 2022). Albeit this stimulation cannot be prevented by experimental measures, whether it is sufficient to generate a SEP is unclear. This activation might be considered similar to that occurring in the dermatomal SEP (dSEP), which are sometimes used in clinical neurophysiology to investigate nerve root sensory function (Date et al., 1988). When obtained by stimulation of the limbs, dSEPs tend to be smaller and less consistent than SEPs obtained by stimulation of large nerve trunks; as a consequence, their use is mostly limited to

within-subject, side to side comparisons (Dikmen and Oge, 2013; Tsai et al., 2012; Tsai et al., 2005). The recording of consistent dSEPs after ES of trigeminal sensory territory is even more difficult and no reliable responses can be recorded with standard techniques (Troni, 2022); the same is probably true for scalp sensory territory. Additionally, no direct evidence exists in this regards, as the most cranial region investigated in this context is the neck (Slimp et al., 1992). At least two considerations could be made against the possibility of obtaining clear dSEP from the scalp area. The first is anatomical: if dSEPs tend to be inconsistent when elicited by ES of densely innervated areas, such as the limbs, this would be even more the case with stimulation of the scalp, where the density of somatosensory fibres is much smaller (Corniani and Saal, 2020). Second, direct evidence for a lack of SEP evoked by TMS comes from studies on patients with brain lesions due to ischemia or trauma. In these studies, the authors found no evidence of EEG responses when TMS was applied on severely damaged, mostly necrotic cortical areas with intact skull and scalp; notably, somatosensory function in these patients was preserved (Gosseries et al., 2015; Sarasso et al., 2020).

3.4. Vibration

Another possible source of somatosensory stimulation by TMS is related to coil-induced vibration on the scalp. This has been suggested to potentially contaminate the TEP, an effect which can be mitigated by the application of a foam layer beneath the coil to dampen its oscillations (Nikouline et al., 1999; ter Braack et al., 2015). It should be noted, however, than input from coil vibration has been interpreted as bone conducted AS, rather that somatosensory activation. This is physiologically plausible, as the frequency of coil vibration is in the range of several KHz, peaking around 10 KHz (Koponen et al., 2021; Koponen et al., 2020; Tiitinen et al., 1999), thus compatible with that of audible sound (Purves et al., 2001). Given the very brief vibration of the coil, it is plausible to hypothesize that only rapidly adapting (RA) skin receptors would be excited by the stimulus (Macefield, 2005). However, the two main classes of RA (RAI and RAII, identified with Meissner's and Pacinian corpuscles, respectively) are preferentially activated by vibration of much lower frequency than that of TMS coils (Konietzny and Hensel, 1977). Additionally, while there is evidence of steady-state SEP elicited by prolonged vibration on the upper limbs (Tobimatsu et al., 1999), there is no evidence that brief trains of vibration can evoke transient EEG responses.

3.5. Activation of pain receptors

Pain has been advocated as a possible source of bias during TMS (Conde et al., 2019). Subjective reports of pain during TMS are largely variable, ranging from its absence (Benecke et al., 1988; Leodori et al., 2022b; Rocchi et al., 2021) to moderate levels (Conde et al., 2019; Gordon et al., 2021). Coil shape, stimulation intensity and individual pain threshold contribute to subjective pain experience during TMS (Holmes and Meteyard, 2018; Meteyard and Holmes, 2018). Coil location is another important factor, with areas far from the vertex, in particular frontal regions, being linked to greater pain perception (Meteyard and Holmes, 2018). However, some disambiguation is necessary. Pain-evoked responses require specialized methods, such as laser, contact heat and intraepidermal ES (Verdugo et al., 2022). With these techniques, it is possible to selectively stimulate skin nociceptors and small fibres carrying pain sensation; this is very different from TMS, which rather activates large-caliber skin fibres (Cros et al., 1990), which carry non-nociceptive somatosensory information. Rather than by activation of pain receptors, it is likely that TMS may cause discomfort due to muscle twitches induced in some experimental settings (see above); this is supported by the very high correlation between subjective perception of pain/annoyance and muscle twitches due to TMS (Meteyard and Holmes, 2018).

3.6. Approximation of putative somatosensory responses due to TMS in the TMS-EEG setting

Despite the many possible sources of somatosensory input generated by TMS, how the latter can contaminate the TEP has been the object of a relatively small number of studies. Most of them used either bipolar ES of the scalp (Conde et al., 2019; Gordon et al., 2018) or magnetic stimulation to the shoulder (Biabani et al., 2021; Biabani et al., 2019) in the context of a so called realistic sham stimulation, i.e., where somatosensory input is coupled with AS from the TMS click, in an attempt to reproduce the global sensory input of TMS as closely as possible. Due to the coupling with AS, these studies do not provide conclusive information on possible SEP generation by TMS, so they are not further considered.

In a recent study by Rocchi and coworkers (Rocchi et al., 2021), bipolar ES of the scalp in the M1 region, applied with a stimulation intensity matching that of somatosensory input by TMS on the same area based on subject's perception, elicited a small positive wave located at the vertex (P200). By increasing the stimulation intensity, the same peak increased in amplitude and a preceding negative wave around 100 ms (N100) appeared at the same location. A similar N100/P200 pattern has been confirmed with higher stimulation intensities at the same location, but with four stimulating electrodes (Gordon et al., 2021). The exclusive role of muscle twitches in the generation of this response is not defined, as they were not controlled for in the first study (Rocchi et al., 2021) and were purposefully elicited in the second (Gordon et al., 2021). Therefore, it is not clear whether the vertex N100/P200 in this context is due to activation of cutaneous somatosensory fibres, to the muscle twitches themselves, or both.

It is very important to note that the mentioned vertex N100/P200 responses are not related to specific, unimodal activation of the S1, as commonly seen after ES of nerve trunks in the limbs, which are contralateral to the stimulated site (Cruccu et al., 2008; Rocchi et al., 2019). Rather, their spatial and temporal distribution is similar to that occurring after pure AS (Rocchi et al., 2021), combined AS and ES of the scalp (Conde et al., 2019; Fernandez et al., 2021; Gordon et al., 2018; Rocchi et al., 2021) or the neck (Fernandez et al., 2021; Fong et al., 2023; Sasaki et al., 2022), magnetic stimulation of the shoulder (Biabani et al., 2021; Biabani et al., 2019), as well as laser and visual stimulation (Mouraux and Iannetti, 2009). Therefore, rather than being a modality-specific response, the vertex N100/P200 is interpretable as a saliency-related multimodal response, due to activation of the anterior cingulate cortex (Tanaka et al., 2008) and possibly reflecting arousal and/or attentional reorientation following external stimuli (Mouraux and Iannetti, 2009; Rocchi et al., 2021). It is to note that this conclusion does not exclude S1 activation, which has been demonstrated by magnetoencephalographic recordings following touch and pressure applied on the face and scalp (Hoshiyama et al., 1995; Yamashita et al., 1999). It is possible to hypothesize that the absence of a clear EEG response following similar somatosensory activation is due to low signal to noise ratio.

4. Conclusions and perspectives

In this review, we broke down possible mechanisms by which the somatosensory input by TMS might generate EEG responses, in an attempt to understand how such stimuli might contaminate "true" TMS-EEG responses, i.e., resulting from direct cortical stimulation. Five sources of somatosensory input were identified based on the available literature: 1) contraction of craniofacial muscle; 2) activation of somatosensory nerve trunks; 3) stimulation of free cutaneous nerve endings; 4) coil vibration; 5) activation of pain receptors. Conclusions are summarized in Fig. 3. We found that there is little physiological evidence to support a role of coil vibration or activation of pain receptors in the generation of TMS-evoked EEG responses. Similarly, there is no evidence in the literature that effective stimulation of purely

Mechanism of somatosensory activation	Occurrence of somatosensory input with TMS	EEG response following TMS	Possible strategies to mitigate EEG responses
Contraction of craniofacial muscle	Yes	Mixed evidence*	Optimize coil positioning, offline removal with ICA
Direct activation of somatosensory nerve trunks	No evidence	No evidence	N/A
Stimulation of free cutaneous nerve endings	Yes	Mixed evidence†	Local anesthetics, offline removal with ICA
Coil vibration	Physiological evidence against	Physiological evidence against	N/A
Activation of pain receptors	Physiological evidence against	Physiological evidence against	N/A

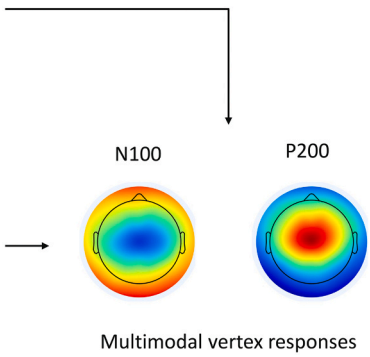

Fig. 3. Summary of current evidence about SEP generation due to somatosensory stimulation of the craniofacial region and possible strategies to mitigate them. * It is not clear whether the vertex N100/P200 observed in some studies is due to muscle twitches, activation of free cutaneous nerve endings, or both. † Activation of free cutaneous nerve endings has been suggested to induce a vertex N100/P200, but this has not been confirmed in TMS studies. See text for details.

somatosensory nerve trunks may occur during TMS; even if it were the case, it is unlikely that this would result in SEPs. By contrast, it is possible that contraction of craniofacial muscle and stimulation of free cutaneous nerve endings give rise to EEG responses, but some caveats should be noted. The first is that the few studies which investigated this issue did not separate the two sources of input (Gordon et al., 2021; Rocchi et al., 2021); therefore, at present, it is not clear whether either or both mechanisms may give rise to EEG responses. Second, the mentioned studies used ES to mimic the somatosensory input of TMS; albeit useful from a practical point of view, this approximation may be incorrect, due to the different sets of nerve fibres activated (Cros et al., 1990). In fact, direct evidence from TMS studies (Gosseries et al., 2015; Sarasso et al., 2020), albeit on relatively small samples of patients with cerebral lesions, seems to suggest that TMS itself does not elicit any EEG responses. Finally, it is important to note that there is no evidence that craniofacial muscle twitches and input from free cutaneous nerves may give rise to SEPs in a strict sense, i.e., due to unimodal activation of the S1; rather, current literature point to the possible generation of vertex N100/P200 potentials, representing multimodal responses.

Having defined the possibility of occurrence and the features of EEG responses to somatosensory input in the craniofacial region, an important question is how to minimize them, thus avoiding their superposition to TEPs. While it is not possible to avoid stimulation of somatosensory skin fibres, craniofacial muscle twitches can be avoided by stimulating medial cortical areas (Meteyard and Holmes, 2018); however, albeit this might be useful in some research settings (Ferrarelli et al., 2008; Napolitani et al., 2014), TMS of more lateral areas might be required to assess questions related to motor (Leodori et al., 2022a; Rocchi et al., 2023) or cognitive (Desforges et al., 2022; Salo et al., 2020) physiology or pathophysiology. In such cases, muscle twitches cannot be avoided; however, it is possible to minimize them by slight rotation of the TMS coil and check for the effectiveness of this procedure based on real-time assessment of TEPs (Casarotto et al., 2022). Despite its usefulness, this technical solution should be applied carefully, as TEPs have been demonstrated to be sensitive to coil rotation (Bonato et al., 2006; Casarotto et al., 2010; Casula et al., 2022a; Casula et al., 2018; de Goede et al., 2018).

Another possible online approach is the use of local anaesthetics. A previous work has shown mixed results on the effect of topical lidocaine cream in reducing discomfort due to repetitive TMS, applied on the dorsolateral prefrontal cortex, in patients affected by depression (Trevino et al., 2011). Based on the evidence we collected, it is likely that this solution would reduce the activation of free somatosensory nerve endings, but would not limit craniofacial muscle contraction, which is responsible for most of the discomfort associated with TMS (Meteyard and Holmes, 2018). Suppression of muscle twitches can be obtained via injections of lidocaine in the proximity of motor nerves (Luo et al., 2020). This may be helpful in limiting EMG activaty due to stimulation of a nerve trunk by TMS, while blockade of intramuscular motor nerve endings would likely be more difficult to obtain. In either case, the procedure is invasive and would probably more suitable for proof of principle studies, rather than routine application in TMS-EEG.

A different approach to deal with possible EEG responses due to somatosensory input could be their offline removal by ICA. This procedure has been applied to vertex potentials evoked by auditory stimulation (Rogasch et al., 2014; Ross et al., 2022). If, as current evidence indicates, these reflect saliency responses due to both auditory and somatosensory stimulation, then the same technique should be effective in minimizing the impact of the second as well. It should be noted, however, that ICA assumptions are rather strict and include independence between components, which cannot be ensured for sensory evoked responses relative to TEPs (Hernandez-Pavon et al., 2023); consequently, the application of ICA to eliminate saliency-related vertex potentials may carry the potential risk of overcorrecting genuine TEPs. It is likely that further empirical evidence is required to establish the routine utility of this procedure.

A more common method to isolate effects specific to TEPs is the introduction of an experimental somatosensory control condition, such as ES, alone or in the context of a so called realistic sham stimulation, which entails the simultaneous delivery of the TMS click. Whether the two types of stimuli should be necessarily used together is unclear. One study found that saliency responses due to ES and AS summate linearly (Rocchi et al., 2021); this leads to the conclusion that ES and AS can be used separately to control for somatosensory and auditory stimulation of

TMS. However, another report found that such an interaction is not linear (Chowdhury et al., 2022); given the small amount of data available, this topic needs further assessment. It should be note that the term "sham" might be misleading here, as ES is clearly perceived differently than TMS (Gordon et al., 2021; Rocchi et al., 2021); therefore, more than mimic the somatosensory input of TMS, ES might represent a useful means to verify, if needed, if any effects attributable to changes in TEPs are, in fact, due to different processing of somatosensory input. A recent attempt to optimize sham stimulation for TMS-EEG entails the application of supramaximal ES to both real and sham stimulation, with the objective of saturating SEPs, and then subtracting the second from the first (Gordon et al., 2021). This method creates a "common" SEPs between the two conditions; therefore, their subtraction should theoretically allow to obtain a TEP not contaminated by somatosensory input. However, supramaximal ES may possibly alter the genuine TEP signature (Gordon et al., 2021; Novembre et al., 2019); therefore, further validation is needed.

In conclusion, current literature points to the notion that only some sources of somatosensory input in the context of TMS may generate EEG responses: these are represented by muscle twitches and, possibly, activation of free cutaneous somatosensory nerve fibres. Direct evidence, however, is lacking due to experimental difficulties in selectively reproducing these inputs. There is also no indication that these sources of activation can elicit specific activation of S1; rather, data available in the literature suggest that only a vertex N100/P200 complex, interpretable as a saliency-related multimodal response, may be obtained. Therefore, as for auditory input and related EEG responses (Fig. 4), careful inspection of signals scalp topography is of paramount importance to detect possible effects of somatosensory stimulation on TEP.

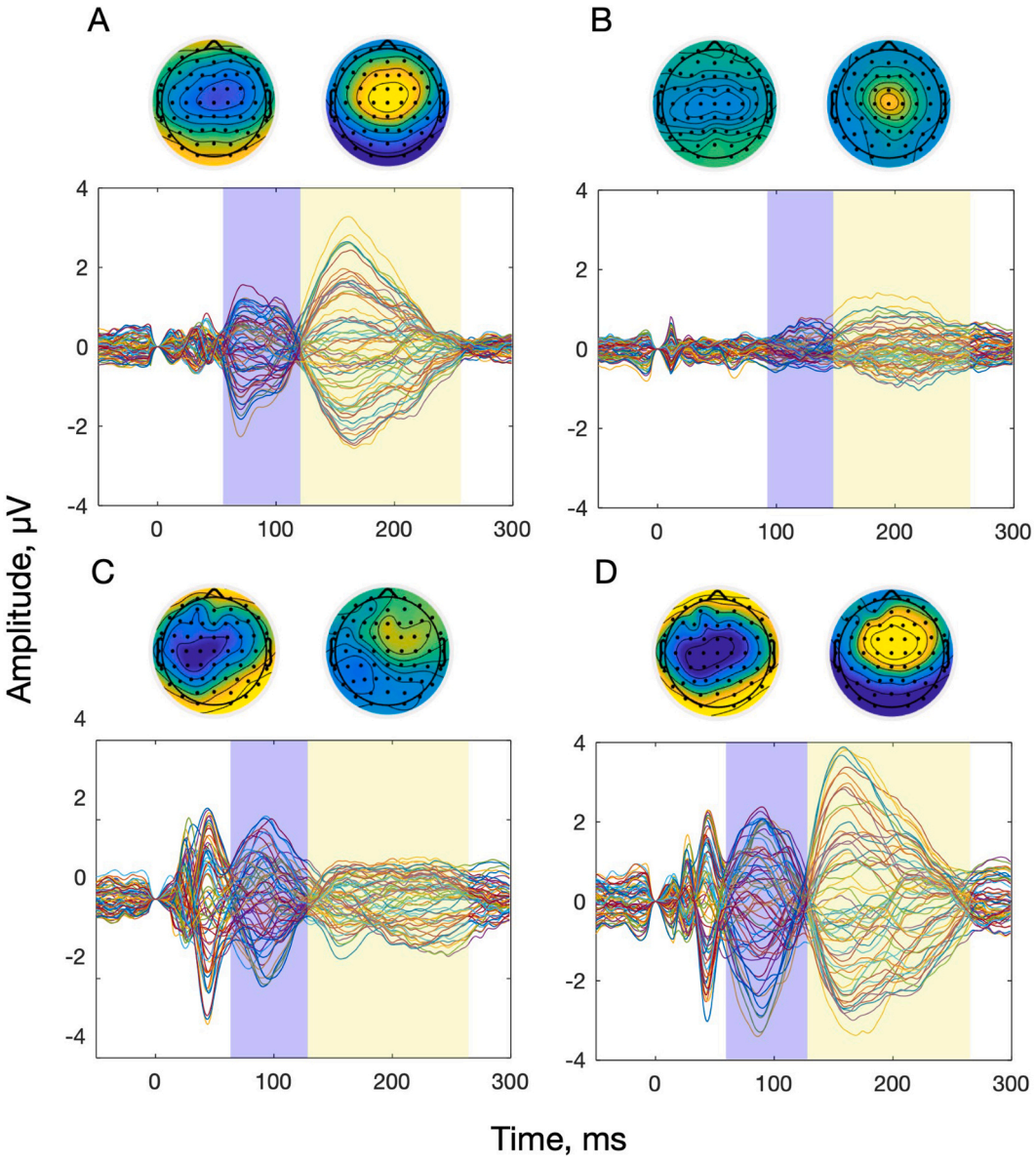

Fig. 4. Multimodal vertex N100/P200 elicited by sensory stimulation and related contamination of the TEP. *Panel A:* vertex N100/P200 elicited by the TMS click alone. *Panel B:* vertex N100/P200 elicited by electrical stimulation of the scalp overlying the left primary motor area, at an intensity of 3 x somatosensory threshold. *Panel C:* TEPs obtained by stimulation of the left primary motor area, with suppression of the TMS click. *Panel D:* TEPs obtained by stimulation of the left primary motor area, without suppression of the TMS click. The butterfly plots depict the average signal of a group of healthy subjects, each line representing signals from a single electrode (63 in total). Average signals in time windows compatible with the vertex N100 (blue panels) and P200 (green panels) are represented by two topographical plots each (left for the N100 and right for the P200).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. E.P.C. was supported by the Italian Ministry of University and Research under the National Recovery and Resilience Plan (Fondi DM 502/2022 – PNRR MC42 Bando Giovani Ricercatori).

Declaration of Competing Interest

None.

References

Arcuri, C., Muzzi, F., Docimo, R., Fusco, E., Pauri, F., Rossini, P.M., 2006. Somatosensory evoked potentials of inferior alveolar nerve. J. Oral. Maxillofac. Surg.: Off. J. Am. Assoc. Oral. Maxillofac. Surg. 64, 594–599.

Badr, G.G., Hanner, P., Edström, S., 1983. Cortical evoked potentials in response to trigeminus nerve stimulation in humans. Clin. EEG (Electroencephalogr.) 14, 61–66.

Benecke, R., Meyer, B.U., Schönle, P., Conrad, B., 1988. Transcranial magnetic stimulation of the human brain: responses in muscles supplied by cranial nerves. Exp. Brain Res. 71, 623–632.

Bennett, M.H., Jannetta, P.J., 1980. Trigeminal evoked potentials in humans. Electroencephalogr. Clin. Neurophysiol. 48, 517–526.

Biabani, M., Fornito, A., Mutanen, T.P., Morrow, J., Rogasch, N.C., 2019. Characterizing and minimizing the contribution of sensory inputs to TMS-evoked potentials. Brain Stimul. 12, 1537–1552.

Biabani, M., Fornito, A., Coxon, J.P., Fulcher, B.D., Rogasch, N.C., 2021. The correspondence between EMG and EEG measures of changes in cortical excitability following transcranial magnetic stimulation. J. Physiol. 599, 2907–2932.

Biondi, A., Rocchi, L., Santoro, V., Rossini, P.G., Beatch, G.N., Richardson, M.P., Premoli, I., 2022. Spontaneous and TMS-related EEG changes as new biomarkers to measure anti-epileptic drug effects. Sci. Rep. 12, 1919.

Bonato, C., Miniussi, C., Rossini, P.M., 2006. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin. Neurophysiol. 117, 1699–1707.

ter Braack, E.M., de Vos, C.C., van Putten, M.J., 2015. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. Brain Topogr. 28, 520–528.

Cao, K.X., Ma, M.L., Wang, C.Z., Iqbal, J., Si, J.J., Xue, Y.X., Yang, J.L., 2021. TMS-EEG: an emerging tool to study the neurophysiologic biomarkers of psychiatric disorders. Neuropharmacology 197, 108574.

Casarotto, S., Romero Lauro, L.J., Bellina, V., Casali, A.G., Rosanova, M., Pigorini, A., Defendi, S., Mariotti, M., Massimini, M., 2010. EEG responses to TMS are sensitive to changes in the perturbation parameters and repeatable over time. PloS One 5, e10281.

Casarotto, S., Fecchio, M., Rosanova, M., Varone, G., D'Ambrosio, S., Sarasso, S., Pigorini, A., Russo, S., Comanducci, A., Ilmoniemi, R.J., Massimini, M., 2022. The rt-TEP tool: real-time visualization of TMS-Evoked Potentials to maximize cortical activation and minimize artifacts. J. Neurosci. Methods 370, 109486.

Casula, E.P., Rocchi, L., Hannah, R., Rothwell, J.C., 2018. Effects of pulse width, waveform and current direction in the cortex: a combined cTMS-EEG study. Brain Stimul. 11, 1063–1070.

Casula, E.P., Maiella, M., Pellicciari, M.C., Porrazzini, F., D'Acunto, A., Rocchi, L., Koch, G., 2020. Novel TMS-EEG indexes to investigate interhemispheric dynamics in humans. Clin. Neurophysiol. 131, 70–77.

Casula, E.P., Pellicciari, M.C., Bonnì, S., Spanò, B., Ponzo, V., Salsano, I., Giulietti, G., Martino Cinnera, A., Maiella, M., Borghi, I., Rocchi, L., Bozzali, M., Sallustio, F., Caltagirone, C., Koch, G., 2021. Evidence for interhemispheric imbalance in stroke patients as revealed by combining transcranial magnetic stimulation and electroencephalography. Hum. Brain Mapp. 42, 1343–1358.

Casula, E.P., Leodori, G., Ibáñez, J., Benussi, A., Rawji, V., Tremblay, S., Latorre, A., Rothwell, J.C., Rocchi, L., 2022a. The effect of coil orientation on the stimulation of the pre-supplementary motor area: a combined TMS and EEG study. Brain Sci. 12.

Casula, E.P., Pellicciari, M.C., Bonnì, S., Borghi, I., Maiella, M., Assogna, M., Minei, M., Motta, C., D'Acunto, A., Porrazzini, F., Pezzopane, V., Mencarelli, L., Roncaioli, A., Rocchi, L., Spampinato, D.A., Caltagirone, C., Santarnecchi, E., Martorana, A., Koch, G., 2022b. Decreased frontal gamma activity in alzheimer disease patients. Ann. Neurol. 92, 464–475.

Chowdhury, N.S., Rogasch, N.C., Chiang, A.K.I., Millard, S.K., Skippen, P., Chang, W.J., Bilska, K., Si, E., Seminowicz, D.A., Schabrun, S.M., 2022. The influence of sensory potentials on transcranial magnetic stimulation - electroencephalography recordings. Clin. Neurophysiol. 140, 98–109.

Cobo, J.L., Abbate, F., de Vicente, J.C., Cobo, J., Vega, J.A., 2017. Searching for proprioceptors in human facial muscles. Neurosci. Lett. 640, 1–5.

Cocito, D., Isoardo, G., Migliaretti, G., Ciaramitaro, P., Rota, E., Poglio, F., Bergamasco, B., 2003. Intracranial stimulation of the facial nerve: normative values with magnetic coil in 240 nerves. Neurol. Sci.: Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 23, 307–311.

Conde, V., Tomasevic, L., Akopian, I., Stanek, K., Saturnino, G.B., Thielscher, A., Bergmann, T.O., Siebner, H.R., 2019. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. NeuroImage 185, 300–312.

Corniani, G., Saal, H.P., 2020. Tactile innervation densities across the whole body. J. Neurophysiol. 124, 1229–1240.

Cristofari, A., De Santis, M., Lucidi, S., Rothwell, J., Casula, E.P., Rocchi, L., 2023. Machine Learning-Based Classification to Disentangle EEG Responses to TMS and Auditory Input 13, 866.

Cros, D., Day, T.J., Shahani, B.T., 1990. Spatial dispersion of magnetic stimulation in peripheral nerves. Muscle Nerve 13, 1076–1082.

Cruccu, G., Aminoff, M.J., Curio, G., Guerit, J.M., Kakigi, R., Mauguiere, F., Rossini, P. M., Treede, R.D., Garcia-Larrea, L., 2008. Recommendations for the clinical use of somatosensory-evoked potentials. Clin. Neurophysiol. 119, 1705–1719.

Cruciani, A., Mancuso, M., Sveva, V., Maccarrone, D., Todisco, A., Motolese, F., Santoro, F., Pilato, F., Spampinato, D.A., Rocchi, L., Di Lazzaro, V., Capone, F., 2023. Using TMS-EEG to assess the effects of neuromodulation techniques: a narrative review. Front. Hum. Neurosci. 17, 1247104.

Date, E.S., Ortega, H.R., Hall, K., Rappaport, M., 1988. Somatosensory evoked responses to dermatomal stimulation in cervical spinal cord injured and normal subjects. Clin. EEG (Electroencephalogr.) 19, 144–154.

Deflorio, D., Di Luca, M., Wing, A.M., 2022. Skin and mechanoreceptor contribution to tactile input for perception: a review of simulation models. Front. Hum. Neurosci. 16, 862344.

Desforges, M., Hadas, I., Mihov, B., Morin, Y., Rochette Braün, M., Lioumis, P., Zomorrodi, R., Théoret, H., Lepage, M., Daskalakis, Z.J., Tremblay, S., 2022. Dose-response of intermittent theta burst stimulation of the prefrontal cortex: a TMS-EEG study. Clin. Neurophysiol. 136, 158–172.

Dikmen, P.Y., Oge, A.E., 2013. Diagnostic use of dermatomal somatosensory-evoked potentials in spinal disorders: case series. J. Spinal Cord. Med. 36, 672–678.

Dubach, P., Guggisberg, A.G., Rösler, K.M., Hess, C.W., Mathis, J., 2004. Significance of coil orientation for motor evoked potentials from nasalis muscle elicited by transcranial magnetic stimulation. Clin. Neurophysiol. 115, 862–870.

Dulak, D., Naqvi, I.A., 2021. Neuroanatomy, Cranial Nerve 7 (Facial), Treasure Island (FL).

Fagade, O.O., Wastell, D.G., 1990. Trigeminal somatosensory evoked potentials: technical parameters, reliability and potential in clinical dentistry. J. Dent. 18, 137–141.

Fernandez, L., Biabani, M., Do, M., Opie, G.M., Hill, A.T., Barham, M.P., Teo, W.P., Byrne, L.K., Rogasch, N.C., Enticott, P.G., 2021. Assessing cerebellar-cortical connectivity using concurrent TMS-EEG: a feasibility study. J. Neurophysiol. 125, 1768–1787.

Ferrarelli, F., Phillips, M.L., 2021. Examining and modulating neural circuits in psychiatric disorders with transcranial magnetic stimulation and electroencephalography: present practices and future developments. Am. J. Psychiatry 178, 400–413.

Ferrarelli, F., Massimini, M., Peterson, M.J., Riedner, B.A., Lazar, M., Murphy, M.J., Huber, R., Rosanova, M., Alexander, A.L., Kalin, N., Tononi, G., 2008. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. Am. J. Psychiatry 165, 996–1005.

Ferreri, F., Rossini, P.M., 2013. TMS and TMS-EEG techniques in the study of the excitability, connectivity, and plasticity of the human motor cortex. Rev. Neurosci. 24, 431–442.

Fong, P.Y., Spampinato, D., Michell, K., Mancuso, M., Brown, K., Ibáñez, J., Santo, A.D., Latorre, A., Bhatia, K., Rothwell, J.C., Rocchi, L., 2023. EEG responses induced by cerebellar TMS at rest and during visuomotor adaptation. NeuroImage 275, 120188.

de Goede, A.A., Ter Braack, E.M., van Putten, M., 2018. Accurate coil positioning is important for single and paired pulse TMS on the subject level. Brain Topogr. 31, 917–930.

Gordon, P.C., Desideri, D., Belardinelli, P., Zrenner, C., Ziemann, U., 2018. Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. Brain Stimul. 11, 1322–1330.

Gordon, P.C., Jovellar, D.B., Song, Y., Zrenner, C., Belardinelli, P., Siebner, H.R., Ziemann, U., 2021. Recording brain responses to TMS of primary motor cortex by EEG - utility of an optimized sham procedure. NeuroImage 245, 118708.

Gosseries, O., Sarasso, S., Casarotto, S., Boly, M., Schnakers, C., Napolitani, M., Bruno, M. A., Ledoux, D., Tshibanda, J.F., Massimini, M., Laureys, S., Rosanova, M., 2015. On the cerebral origin of EEG responses to TMS: insights from severe cortical lesions. Brain Stimul. 8, 142–149.

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L.G., Mall, V., Kaelin-Lang, A., Mima, T., Rossi, S., Thickbroom, G.W., Rossini, P.M., Ziemann, U., Valls-Solé, J., Siebner, H.R., 2012. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin. Neurophysiol. 123, 858–882.

Hallett, M., 2007. Transcranial magnetic stimulation: a primer. Neuron 55, 187–199.

Hernandez-Pavon, J.C., Veniero, D., Bergmann, T.O., Belardinelli, P., Bortoletto, M., Casarotto, S., Casula, E.P., Farzan, F., Fecchio, M., Julkunen, P., Kallioniemi, E., Lioumis, P., Metsomaa, J., Miniussi, C., Mutanen, T.P., Rocchi, L., Rogasch, N.C., Shafi, M.M., Siebner, H.R., Thut, G., Zrenner, C., Ziemann, U., Ilmoniemi, R.J., 2023. TMS combined with EEG: Recommendations and open issues for data collection and analysis. Brain Stimul. 16, 567–593.

Hogan, Q.H., Abram, S.E., 1997. Neural blockade for diagnosis and prognosis. A Rev. Anesthesiol. 86, 216–241.

Holmes, N.P., Meteyard, L., 2018. Subjective discomfort of TMS predicts reaction times differences in published studies. Front. Psychol. 9, 1989.

Hordacre, B., Ghosh, R., Goldsworthy, M.R., Ridding, M.C., 2019. Transcranial magnetic stimulation-EEG biomarkers of poststroke upper-limb motor function. J. Stroke Cerebrovasc. Dis.: Off. J. Natl. Stroke Assoc. 28, 104452.

Hoshiyama, M., Kakigi, R., Koyama, S., Kitamura, Y., Shimoio, M., Watanabe, S., 1995. Somatosensory evoked magnetic fields after mechanical stimulation of the scalp in humans. Neurosci. Lett. 195, 29–32.

Huff, T., Daly, T.T., 2021. Neuroanatomy, Cranial Nerve 5 (Trigeminal), Treasure Island (FL).
Ilmoniemi, R.J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H.J., Näätänen, R., Katila, T., 1997. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 8, 3537–3540.
Keser, Z., Buchl, S.C., Seven, N.A., Markota, M., Clark, H.M., Jones, D.T., Lanzino, G., Brown Jr., R.D., Worrell, G.A., Lundstrom, B.N., 2022. Electroencephalogram (EEG) with or without transcranial magnetic stimulation (TMS) as biomarkers for post-stroke recovery: a narrative review. Front. Neurol. 13, 827866.
Konietzny, F., Hensel, H., 1977. Response of rapidly and slowly adapting mechanoreceptors and vibratory sensitivity in human hairy skin. Pflug. Arch.: Eur. J. Physiol. 368, 39–44.
Koponen, L.M., Goetz, S.M., Tucci, D.L., Peterchev, A.V., 2020. Sound comparison of seven TMS coils at matched stimulation strength. Brain Stimul. 13, 873–880.
Koponen, L.M., Goetz, S.M., Peterchev, A.V., 2021. Double-containment coil with enhanced winding mounting for transcranial magnetic stimulation with reduced acoustic noise. IEEE Trans. Bio-Med. Eng. 68, 2233–2240.
Leodori, G., De Bartolo, M.I., Guerra, A., Fabbrini, A., Rocchi, L., Latorre, A., Paparella, G., Belvisi, D., Conte, A., Bhatia, K.P., Rothwell, J.C., Berardelli, A., 2022a. Motor cortical network excitability in Parkinson's disease. Mov. Disord.: Off. J. Mov. Disord. Soc. 37, 734–744.
Leodori, G., Rocchi, L., Mancuso, M., De Bartolo, M.I., Baione, V., Costanzo, M., Belvisi, D., Conte, A., Defazio, G., Berardelli, A., 2022b. The effect of stimulation frequency on transcranial evoked potentials. Transl. Neurosci. 13, 211–217.
Luo, J., Cai, G., Ling, D., Zhang, N., Chen, X., Cao, X., Yu, B., 2020. Mean effective volume of local anesthetics by nerve conduction technique. Ann. Transl. Med. 8, 174.
Macaluso, G.M., Pavesi, G., Bonanini, M., Mancia, D., Gennari, P.U., 1990. Motor-evoked potentials in masseter muscle by electrical and magnetic stimulation in intact alert man. Arch. Oral. Biol. 35, 623–628.
Maccabee, P.J., Amassian, V.E., Cracco, R.Q., Cracco, J.B., Anziska, B.J., 1988. Intracranial stimulation of facial nerve in humans with the magnetic coil. Electroencephalogr. Clin. Neurophysiol. 70, 350–354.
Macefield, V.G., 2005. Physiological characteristics of low-threshold mechanoreceptors in joints, muscle and skin in human subjects. Clin. Exp. Pharmacol. Physiol. 32, 135–144.
Mancuso, M., Sveva, V., Cruciani, A., Brown, K., Ibáñez, J., Rawji, V., Casula, E., Premoli, I., D'Ambrosio, S., Rothwell, J., Rocchi, L., 2021. Transcranial evoked potentials can be reliably recorded with active electrodes. Brain Sci. 11.
Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., Tononi, G., 2005. Breakdown of cortical effective connectivity during sleep. Sci. (N. Y. N. Y.) 309, 2228–2232.
Meteyard, L., Holmes, N.P., 2018. TMS SMART - scalp mapping of annoyance ratings and twitches caused by transcranial magnetic stimulation. J. Neurosci. Methods 299, 34–44.
Mima, T., Terada, K., Maekawa, M., Nagamine, T., Ikeda, A., Shibasaki, H., 1996. Somatosensory evoked potentials following proprioceptive stimulation of finger in man. Exp. Brain Res. 111, 233–245.
Mouraux, A., Iannetti, G.D., 2009. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J. Neurophysiol. 101, 3258–3269.
Mutanen, T., Mäki, H., Ilmoniemi, R.J., 2013. The effect of stimulus parameters on TMS-EEG muscle artifacts. Brain Stimul. 6, 371–376.
Napolitani, M., Bodart, O., Canali, P., Seregni, F., Casali, A., Laureys, S., Rosanova, M., Massimini, M., Gosseries, O., 2014. Transcranial magnetic stimulation combined with high-density EEG in altered states of consciousness. Brain Inj. 28, 1180–1189.
Nardone, R., Sebastianelli, L., Versace, V., Ferrazzoli, D., Saltuari, L., Trinka, E., 2021. TMS-EEG co-registration in patients with mild cognitive impairment, Alzheimer's disease and other dementias: a systematic review. Brain Sci. 11.
Niddam, D.M., Chen, L.F., Wu, Y.T., Hsieh, J.C., 2005. Spatiotemporal brain dynamics in response to muscle stimulation. NeuroImage 25, 942–951.
Nikouline, V., Ruohonen, J., Ilmoniemi, R.J., 1999. The role of the coil click in TMS assessed with simultaneous EEG. Clin. Neurophysiol. 110, 1325–1328.
Novembre, G., Pawar, V.M., Kilintari, M., Bufacchi, R.J., Guo, Y., Rothwell, J.C., Iannetti, G.D., 2019. The effect of salient stimuli on neural oscillations, isometric force, and their coupling. NeuroImage 198, 221–230.
Paus, T., Sipila, P.K., Strafella, A.P., 2001. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J. Neurophysiol. 86, 1983–1990.
Pokorny, L., Jarczok, T.A., Bender, S., 2022. Topography and lateralization of long-latency trigeminal somatosensory evoked potentials. Clin. Neurophysiol. 135, 37–50.
Purves, D., Augustine, G.J., Fitzpatrick, D., 2001. Neuroscience. Sinauer Associates, Sunderland (MA).
Rawji, V., Kaczmarczyk, I., Rocchi, L., Fong, P.Y., Rothwell, J.C., Sharma, N., 2021. Preconditioning stimulus intensity alters paired-pulse TMS evoked potentials. Brain Sci. 11.
Rocchi, L., Ibáñez, J., Benussi, A., Hannah, R., Rawji, V., Casula, E., Rothwell, J., 2018. Variability and predictors of response to continuous theta burst stimulation: a TMS-EEG study. Front. Neurosci. 12, 400.
Rocchi, L., Latorre, A., Ibanez Pereda, J., Spampinato, D., Brown, K.E., Rothwell, J., Bhatia, K., 2019. A case of congenital hypoplasia of the left cerebellar hemisphere and ipsilateral cortical myoclonus. Mov. Disord.: Off. J. Mov. Disord. Soc. 34, 1745–1747.
Rocchi, L., Di Santo, A., Brown, K., Ibáñez, J., Casula, E., Rawji, V., Di Lazzaro, V., Koch, G., Rothwell, J., 2021. Disentangling EEG responses to TMS due to cortical and peripheral activations. Brain Stimul. 14, 4–18.
Rocchi, L., Spampinato, D.A., Pezzopane, V., Orth, M., P.S, B., Rothwell, J.C., Casula, E. P., 2023. Cerebellar noninvasive neuromodulation influences the reactivity of the contralateral primary motor cortex and surrounding areas: a TMS-EMG-EEG study. Cerebellum (London, England) 22, 319–331.
Rödel, R., Laskawi, R., Markus, H., Neupert, P., 1999. Possible one-dimensional determination of cortical representative fields of mimetic lower lip muscles by transcranial magnetic stimulation. Laryngo- Rhino- Otol. 78, 552–556.
Rogasch, N.C., Thomson, R.H., Farzan, F., Fitzgibbon, B.M., Bailey, N.W., Hernandez-Pavon, J.C., Daskalakis, Z.J., Fitzgerald, P.B., 2014. Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. NeuroImage 101, 425–439.
Ross, J.M., Ozdemir, R.A., Lian, S.J., Fried, P.J., Schmitt, E.M., Inouye, S.K., Pascual-Leone, A., Shafi, M.M., 2022. A structured ICA-based process for removing auditory evoked potentials. Sci. Rep. 12, 1391.
Russo, S., Sarasso, S., Puglisi, G.E., Dal Palù, D., Pigorini, A., Casarotto, S., D'Ambrosio, S., Astolfi, A., Massimini, M., Rosanova, M., Fecchio, M., 2022. TAAC - TMS adaptable auditory control: a universal tool to mask TMS clicks. J. Neurosci. Methods 370, 109491.
Salo, K.S., Mutanen, T.P., Vaalto, S.M.I., Ilmoniemi, R.J., 2020. EEG artifact removal in TMS studies of cortical speech areas. Brain Topogr. 33, 1–9.
Sand, T., Becser, N., 1998. Neurophysiological and anatomical variability of the greater auricular nerve. Acta Neurol. Scand. 98, 333–339.
Sarasso, S., D'Ambrosio, S., Fecchio, M., Casarotto, S., Viganò, A., Landi, C., Mattavelli, G., Gosseries, O., Quarenghi, M., Laureys, S., Devalle, G., Rosanova, M., Massimini, M., 2020. Local sleep-like cortical reactivity in the awake brain after focal injury. Brain: J. Neurol. 143, 3672–3684.
Sasaki, R., Hand, B.J., Liao, W.Y., Rogasch, N.C., Fernandez, L., Semmler, J.G., Opie, G. M., 2022. Utilising TMS-EEG to Assess the Response to Cerebellar-Brain Inhibition. Cerebellum (London, England).
Schmid, U.D., Møller, A.R., Schmid, J., 1992. The excitation site of the trigeminal nerve to transcranial magnetic stimulation varies and lies proximal or distal to the foramen ovale: an intraoperative electrophysiological study in man. Neurosci. Lett. 141, 265–268.
Schmid, U.D., Møller, A.R., Schmid, J., 1995. Transcranial magnetic stimulation of the trigeminal nerve: intraoperative study on stimulation characteristics in man. Muscle Nerve 18, 487–494.
Schriefer, T.N., Mills, K.R., Murray, N.M., Hess, C.W., 1988. Evaluation of proximal facial nerve conduction by transcranial magnetic stimulation. J. Neurol. Neurosurg. Psychiatry 51, 60–66.
Seiss, E., Hesse, C.W., Drane, S., Oostenveld, R., Wing, A.M., Praamstra, P., 2002. Proprioception-related evoked potentials: origin and sensitivity to movement parameters. NeuroImage 17, 461–468.
Seki, Y., Krain, L., Yamada, T., Kimura, J., 1990. Transcranial magnetic stimulation of the facial nerve: recording technique and estimation of the stimulated site. Neurosurgery 26, 286–290.
Slimp, J.C., Rubner, D.E., Snowden, M.L., Stolov, W.C., 1992. Dermatomal somatosensory evoked potentials: cervical, thoracic, and lumbosacral levels. Electroencephalogr. Clin. Neurophysiol. 84, 55–70.
Tanaka, E., Inui, K., Kida, T., Miyazaki, T., Takeshima, Y., Kakigi, R., 2008. A transition from unimodal to multimodal activations in four sensory modalities in humans: an electrophysiological study. BMC Neurosci. 9, 116.
Tiitinen, H., Virtanen, J., Ilmoniemi, R.J., Kamppuri, J., Ollikainen, M., Ruohonen, J., Näätänen, R., 1999. Separation of contamination caused by coil clicks from responses elicited by transcranial magnetic stimulation. Clin. Neurophysiol. 110, 982–985.
Tobimatsu, S., Zhang, Y.M., Kato, M., 1999. Steady-state vibration somatosensory evoked potentials: physiological characteristics and tuning function. Clin. Neurophysiol. 110, 1953–1958.
Tokimura, H., Tokimura, Y., Asakura, T., 1993. Transcranial magnetic stimulation of facial nerve with a figure 8 coil. Muscle Nerve 16, 882–883.
Trevino, K., McClintock, S.M., Husain, M.M., 2011. The use of topical lidocaine to reduce pain during repetitive transcranial magnetic stimulation for the treatment of depression. J. ECT 27, 44–47.
Troni, W., 2022. Stimulus artifact removal to detect trigeminal sensory evoked potentials. Clin. Neurophysiol. Pract. 7, 34–41.
Troni, W., Cantello, R., Rainero, I., 1983. Conduction velocity along human muscle fibers in situ. Neurology 33, 1453–1459.
Tsai, S.W., Tsai, C.L., Wu, P.T., Wu, C.Y., Liu, C.L., Jou, I.M., 2012. Intraoperative use of somatosensory-evoked potential in monitoring nerve roots. J. Clin. Neurophysiol.: Off. Publ. Am. Electroencephalogr. Soc. 29, 110–117.
Tsai, T.M., Tsai, C.L., Lin, T.S., Lin, C.C., Jou, I.M., 2005. Value of dermatomal somatosensory evoked potentials in detecting acute nerve root injury: an experimental study with special emphasis on stimulus intensity. Spine 30, E540–E546.
Tsuboyama, M., Kaye, H.L., Rotenberg, A., 2020. Review of transcranial magnetic stimulation in epilepsy. Clin. Ther. 42, 1155–1168.
Verdugo, R.J., Matamala, J.M., Inui, K., Kakigi, R., Valls-Solé, J., Hansson, P., Nilsen, K. B., Lombardi, R., Lauria, G., Petropoulos, I.N., Malik, R.A., Treede, R.D., Baumgärtner, U., Jara, P.A., Campero, M., 2022. Review of techniques useful for the assessment of sensory small fiber neuropathies: report from an IFCN expert group. Clin. Neurophysiol. 136, 13–38.
Welter, L., Bramke, S., May, C.A., 2022. Human frontalis muscle innervation and morphology. Plast. Reconstr. Surg. Glob. Open 10, e4200.

Westbrook, K.E., Nessel, T.A., Hohman, M.H., Varacallo, M., 2022. Anatomy, Head and Neck: Facial Muscles, Treasure Island (FL).

Yamashita, H., Kumamoto, Y., Nakashima, T., Yamamoto, T., Inokuchi, A., Komiyama, S., 1999. Magnetic sensory cortical responses evoked by tactile stimulations of the human face, oral cavity and flap reconstructions of the tongue. Eur. Arch. Oto-Rhino-Laryngol.: Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. (EUFOS): Affil. Ger. Soc. Oto-Rhino-Laryngol. - Head. Neck Surg. 256 (Suppl 1), S42–S46.

Zrenner, B., Zrenner, C., Gordon, P.C., Belardinelli, P., McDermott, E.J., Soekadar, S.R., Fallgatter, A.J., Ziemann, U., Müller-Dahlhaus, F., 2020. Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS. Brain Stimul. 13, 197–205.