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REVIEW ARTICLE

Transcranial magnetic stimulation-evoked electroencephalography responses as biomarkers for epilepsy: A review of study design and outcomes

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Abstract

Transcranial magnetic stimulation (TMS) with electroencephalography (EEG), that is TMS-EEG, may assist in managing epilepsy. We systematically reviewed the quality of reporting and findings in TMS-EEG studies on people with epilepsy and healthy controls, and on healthy individuals taking anti-seizure medication. We searched the Cochrane Library, Embase, PubMed and Web of Science databases for original TMS-EEG studies comparing people with epilepsy and healthy controls, and healthy subjects before and after taking anti-seizure medication. Studies should involve quantitative analyses of TMS-evoked EEG responses. We evaluated the reporting of study population characteristics and TMS-EEG protocols (TMS sessions and equipment, TMS trials and EEG protocol), assessed the variation between protocols, and recorded the main TMS-EEG findings. We identified 20 articles reporting 14 unique study populations and TMS methodologies. The median reporting rate for the group of people with epilepsy parameters was 3.5/7 studies and for the TMS parameters was 13/14 studies. TMS protocols varied between studies. Fifteen out of 28 anti-seizure medication trials in total were evaluated with time-domain analyses of single-pulse TMS-EEG data. Anti-seizure medication significantly increased N45, and decreased N100 and P180 component amplitudes but in marginal numbers (N45: 8/15, N100: 7/15, P180: 6/15). Eight articles compared people with epilepsy and controls using different analyses, thus limiting comparability. The reporting quality and methodological uniformity between studies evaluating TMS-EEG as an epilepsy biomarker is poor. The inconsistent findings question the validity of TMS-EEG as an epilepsy biomarker. To demonstrate TMS-EEG clinical applicability, methodology and reporting standards are required.

KEYWORDS
anti-seizure medication, evoked potential, non-invasive, pharmaco-electroencephalography

1 | INTRODUCTION

Transcranial magnetic stimulation (TMS) was introduced almost four decades ago (Barker et al., 1985), paving the way for the non-invasive and pain-free assessment of cortical function in brain disorders (Smith & Stinear, 2016; Tremblay et al., 2019). Cortical responses to TMS pulses likely reflect cortical excitability, generally interpreted as the magnitude of the neuronal response to a received stimulus and reflective of the balance between excitatory and inhibitory dynamics. Alterations in cortical excitability are considered at the core of the disease in focal (Cantello et al., 2000), and generalised epilepsies (Brodtmann et al., 1999). Hence, by examining cortical excitability, TMS might provide biomarkers to distinguish people with epilepsy from healthy controls and to monitor response to anti-seizure medication.

Neurophysiological responses to TMS can be assessed using concomitant electromyography (EMG) – TMS-EMG. This technique, however, has several disadvantages, such as the involvement of the entire corticospinal tract and the potential influence of voluntary behaviour on the TMS motor evoked potentials (Izumi et al., 1995; Kiers et al., 1997). Recently, interest has gradually shifted towards concurrent electroencephalography (EEG) recordings during TMS – TMS-EEG. The prompt EEG response to a TMS pulse approximates cortical responsiveness more closely than TMS-EMG. The two main TMS-EEG parameters are the phase-locked EEG response to a TMS pulse, designated the TMS-evoked EEG potential (TEP), and the oscillatory, not-phase locked TMS-EEG response labelled as TMS-induced oscillations (TIO). Short-latency TEP components seem to mostly mirror genuine cortical reactivity at or in the vicinity of the TMS target. Delayed components such as the N100 and P180 peaks are, however, typically modulated by the interference of secondary responses, for example in the somatosensory circuits (Ahn & Fröhlich, 2021; Sulcova et al., 2022). These observations may promote the use of early over late components for exploring locally enhanced or pharmacologically modulated cortical excitability in epilepsy. Nonetheless, adequate masking of the auditory evoked potential (AEP) facilitates evaluation of delayed cortical responses to the magnetic field (ter Braack et al., 2015), supporting their application as supplementary markers of cortical excitability, both locally and on global scales (Du et al., 2017; Roos et al., 2021). Investigation of TIO allows the characterisation of rhythmic changes to TMS and can be employed as markers of response to anti-seizure medications (Biondi et al., 2022). Interestingly, early phase synchronisation was found to be linearly dependent on stimulation intensities thus offering an attractive alternative to conventional EMG based cortical excitability markers that may be flawed by spinal excitability (Saari et al., 2018).

To assess the potential of TMS-EEG for characterising people with epilepsy and monitoring the treatment response to anti-seizure medication, consistent reporting and employment of methodological parameters, and consistent findings across studies are essential. We systematically reviewed the evidence on TMS-evoked EEG responses as potential epilepsy biomarkers to evaluate these aspects.

2 | METHODS

2.1 | Search procedure

We conducted a systematic review following PRISMA reporting guidelines (Moher et al., 2015). We performed a structured search of the Cochrane Library, Embase, PubMed and Web of Science databases on February 18, 2022. No limiters or filters were used. Briefly, we combined terms associated with, or being synonyms of, TMS, EEG and epilepsy (treatment) in our search entry (Table S1). Duplicates within and across database results were automatically removed. From the remaining records, a primary selection of articles potentially eligible for inclusion was made based on titles and abstracts. This selection was divided between two authors (S.R.G. and D.J.), independently assessing corresponding full-texts for eligibility. Decisions were independently cross-validated by two other authors (R.D.T. and S.B.). In case of disagreement, a consensus was reached after discussion. We also screened reference lists and articles citing the inclusions to find additional articles meeting our selection criteria.

2.2 | Inclusion and exclusion criteria

In the selection process, articles had to fulfil the following criteria: (1) describing a study performed on humans, (2) written in English, (3) describing the original research, (4) peer-reviewed, (5) reporting on subjects with any epilepsy type and control subjects, or on healthy individuals who received anti-seizure medication, and (6) reporting quantitative analysis of immediate EEG responses to TMS. Commentaries, reviews, meta-analyses, and articles presenting only study protocols were excluded. We applied an additional selection criterion to articles reporting results from identical cohorts and acquired by identical TMS interventions but with different data analyses. We only considered the first article in our analysis of the quality of reporting of the study populations and TMS-EEG protocols but also considered successive articles in the analysis of the TMS findings.

2.3 | Data extraction and analysis

We selected study parameters applicable to TMS-EEG studies from a checklist for assessing the methodological quality of TMS-EMG studies (Chipchase et al., 2012). Subject attention was not included as it is difficult to evaluate quantitatively during TMS-EEG experiments. We supplemented the initial selection with parameters deemed applicable to studies conducted on people with epilepsy (aetiology, comorbidities, seizure types, seizure control, last seizure-TMS interval, magnetic resonance imaging [MRI] findings), additional TMS parameters (TMS timing of the day, coil-click sound masking, stimulus type, TMS-EMG acquisition), and EEG protocol parameters (filtering, electrode

TABLE 1 Methodological parameters assessed for quality of reporting.

	TMS-EEG protocol		
Study population	**TMS sessions and equipment**	**TMS trials[a]**	**EEG protocol**
Age	TMS timing of the day	Stimulus intensity[b]	Filtering
Gender	Time between testing days[a]	Stimulus target[b]	Electrode reference
Handedness	Stimulator type[b]	Stimulus type[b]	Electrode type
NI medication use	Coil type[b]	Pulse waveform[b]	Sampling rate
Neurological or psychiatric conditions	Coil diameter[b]	Paired-pulse interval[c]	
Aetiology[d]	Coil orientation	Inter-trial interval	
Comorbidities[d]	Coil positioning[b]	Number of trials per averaged response[b]	
Seizure types[d]	Coil-induced current direction[b]	TMS-EMG acquisition	
Seizure control[d]	Coil click sound masking[b]		
Last seizure-TMS interval[d]			
MRI findings[d]			

Abbreviations: EEG, electroencephalography; EMG, electromyography; MRI, magnetic resonance imaging; NI, non-investigational; TMS, transcranial magnetic stimulation.

[a]Assessed for studies with serial experiments only.

[b]Categorical parameters, as well as coil diameter and number of trials per averaged response, additionally assessed for the number of reporting studies per parameter value.

[c]Assessed for studies applying paired-pulse TMS only.

[d]Assessed for studies on people with epilepsy only.

reference, electrode type, sampling rate). The final selection of parameters for which the quality of reporting among studies was assessed, is provided in Table 1. Per parameter, we counted the number of reporting studies, after which we evaluated the overall quality of reporting by estimating the median number of reporting studies across subsets of study population parameters and TMS-EEG protocol parameters applicable to all studies. For the categorical TMS-EEG parameters applicable to all studies, we additionally counted the number of reporting studies per parameter value. The TMS coil diameter and the number of trials per (subject-)averaged response were also assessed. The latter was divided into fewer than or at least 80 trials, based on a threshold value for which the optimal inter-subject repeatability of the TEP saturates (Kerwin et al., 2018).

For each study, we also recorded the main findings. We ignored TMS-evoked EEG responses in people with conditions other than epilepsy. We divided response parameters into those analysed in the time domain (either amplitudes of canonical TEP components, i.e. N15/P25/P30, N45, P60/70, N100 and P180, or alternative characteristics such as the global field power) and in the frequency domain (TIO in the delta, theta, alpha, beta and gamma EEG frequency bands). We summed the number of studies reporting a particular effect of anti-seizure medication in healthy individuals or the type of subject (epilepsy vs. controls) for each response parameter. We only considered findings evaluated with formal statistical tests.

2.4 | Data and code availability statement

Not applicable to this review article.

3 | RESULTS

3.1 | Selection procedure

We selected 28 of 515 records for full-text screening. Five articles were not eligible as they did not include controls. Four were excluded as they did not report instant TMS-EEG responses (Figure 1). We eventually had 19 articles. Still, citation tracking identified one additional piece, resulting in 20 articles in the final set. Fourteen articles remained after correcting for duplicate cohorts and TMS interventions.

3.2 | Reporting of the study population and transcranial magnetic stimulation-electroencephalography protocol

Half of the studies were conducted on people with epilepsy and healthy controls, and the remainder only on healthy individuals. A median of 12/14 articles reported study population items applicable to all TMS-EEG studies, that is age, gender, handedness, use of non-investigational medication, and presence of neurological or psychiatric conditions in healthy subjects (Table 2). Study population parameters applicable to studies on people with epilepsy only were reported by a median of 3.5/7 articles. Comorbidities (reported by 1/7 articles), seizure types (3/7 articles) and MRI findings (3/7 articles) were the least mentioned items.

In the report of TMS-EEG protocol parameters, electrode type was not mentioned at all, while filtering (5/14 articles), electrode

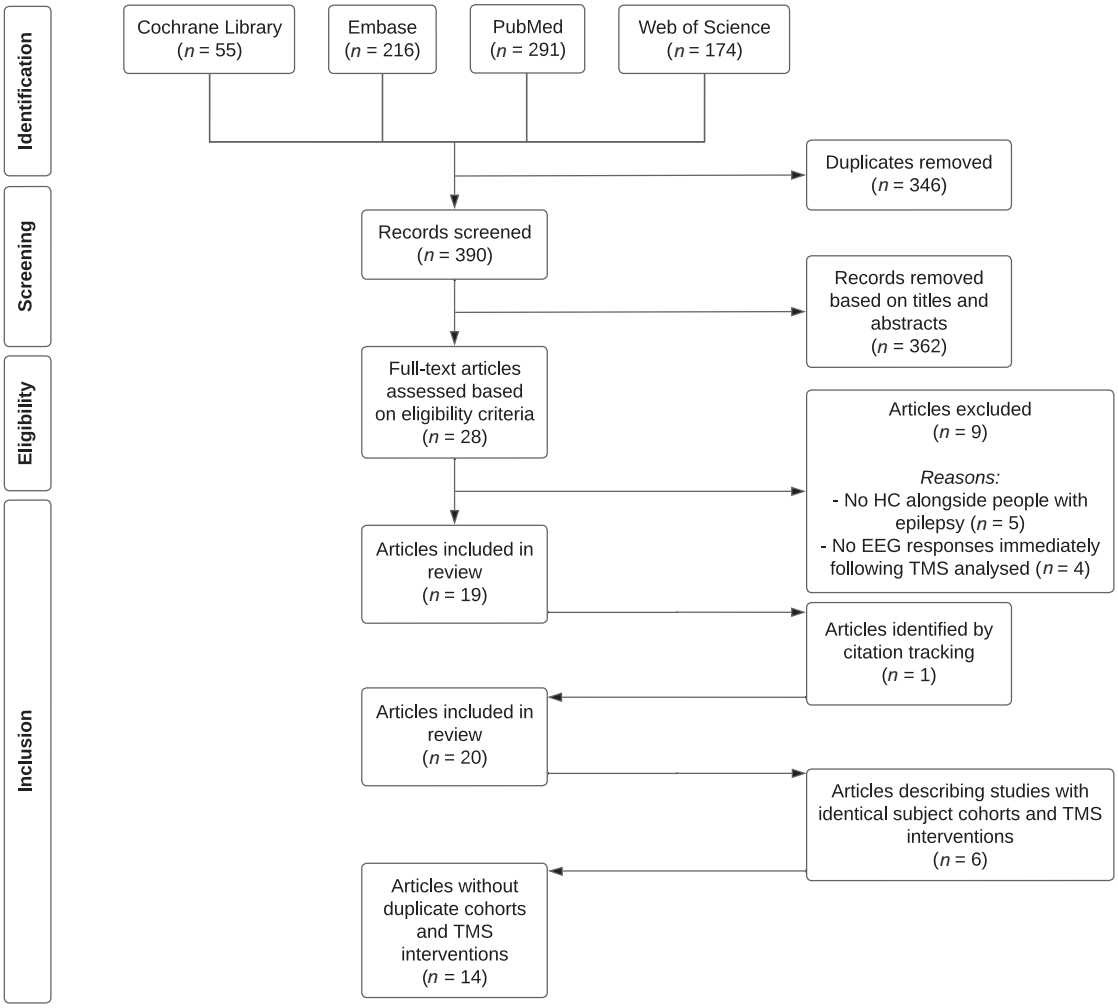

FIGURE 1 Search and inclusion procedure. Flowchart describing the search and inclusion strategy. EEG, electroencephalography; HC, healthy controls; TMS, transcranial magnetic stimulation.

reference (5/14 articles) and TMS timing of the day (5/14 articles) were mentioned by fewer than half of the articles. More than half the articles reported on the remaining parameters that applied to all studies, leading to a median of 13/14 mentions per item (Table 3). We observed variable values across the studies for the TMS-EEG protocol parameters (Table 4).

3.3 | Main transcranial magnetic stimulation-electroencephalography findings

3.3.1 | Studies on healthy individuals only

Twelve articles reported on the modulation of TMS-evoked EEG responses following the use of a one-off dose of an anti-seizure medication by healthy individuals (Table 5). They described 15 evaluations in which single-pulse (SP) responses and five in which paired-pulse (PP) responses were analysed in the time domain. Increased N45, and decreased N100 and P180 TEP component amplitudes were the most reported statistically significant SP stimulation findings (N45: 8/15 evaluations, N100: 7/15 evaluations, P180: 6/15 evaluations). Regarding PP stimulation, suppressed intracortical inhibition of the N100 amplitude was the only evident medication effect (4/5 evaluations). TIO showed diminished medication-induced power in the delta, theta, alpha and beta EEG bands, though only supported by small numbers of evaluations (delta: 2/3 evaluations, theta: 3/5 evaluations, alpha: 4/8, beta: 4/8 evaluations). TIO power in the alpha band, however, was reported to increase after anti-seizure medication in 3/8 evaluations.

3.3.2 | Studies on people with epilepsy and healthy controls

Eight articles described studies' findings in people with epilepsy and healthy controls (Table 6). These studies addressed a wider variety of TMS-evoked EEG response parameters than studies only on healthy individuals. TEP components N100 and P180 were most often

TABLE 2 Reporting of study population parameters by all included studies.

	Valentin et al. (2008)	Del Felice et al. (2011)	Julkunen et al. (2013)	Shafi et al. (2015)	Ter Braack et al. (2016)	Kimiskidis et al. (2017)	Bauer et al. (2019)	Premoli, Castellanos, et al. (2014)	Premoli, Biondi, et al. (2017)	Premoli et al. (2018)	Darmani et al. (2019)	Premoli et al. (2019)	Belardinelli et al. (2021)	Ruijs et al. (2022)	Proportion of reporting studies
Age[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Gender[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Handedness[a]	x	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	12/14
NI medication use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x	✓	✓	12/14
Neurological or psychiatric conditions[b]	x	✓	x	✓	x	x	✓	✓	✓	✓	✓	x	✓	✓	9/14
Aetiology	✓	✓	✓	✓	✓	✓	✓	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	7/7
Comorbidities	x	✓	x	x	x	x	x	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	1/7
Seizure types	✓	x	x	x	x	✓	✓	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	3/7
Seizure control	✓	x	x	✓	✓	✓	✓	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	5/7
Last seizure-TMS interval	✓	x	x	x	✓	✓	✓	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	4/7
MRI findings	✓	x	x	✓	✓	x	x	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	3/7

Note: Only the first of the articles describing studies with identical study populations and transcranial magnetic stimulation interventions is mentioned. ✓ = reported. x = not reported.

Abbreviations: MRI, magnetic resonance imaging; N.A., not applicable; NI, non-investigational; TMS, transcranial magnetic stimulation.

[a]Assessed for reporting of, or control for, age (mean, median or range), gender (distribution) or handedness (distribution) per study group.

[b]Assessed for study groups of healthy subjects and of healthy controls.

TABLE 3 Reporting of transcranial magnetic stimulation (TMS) protocol parameters by all studies.

	Valentin et al. (2008)	Del Felice et al. (2011)	Julkunen et al. (2013)	Shafi et al. (2015)	Ter Braack et al. (2016)	Kimiskidis et al. (2017)	Bauer et al. (2019)	Premoli, Castellanos, et al. (2014)	Premoli, Biondi, et al. (2017)	Premoli et al. (2018)	Darmani et al. (2019)	Premoli et al. (2019)	Belardinelli et al. (2021)	Ruijs et al. (2022)	Proportion of reporting studies
TMS sessions and equipment															
TMS timing of the day	x	✓	x	x	x	✓	✓	x	x	x	✓	x	x	✓	5/14
Time between testing days	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	✓	✓	✓	✓	✓	✓	✓	7/7
Stimulator type	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Coil type	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Coil diameter	✓	x	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	11/14
Coil orientation	x	✓	✓	✓	✓	N.A.[a]	N.A.[a]	✓	✓	x	✓	x	✓	✓	9/12
Coil positioning	x	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	13/14
Coil-induced current direction	x	✓	✓	x	x	x	✓	✓	✓	x	✓	x	✓	x	7/14
Coil click sound masking	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	13/14
TMS trials															
Stimulus intensity	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	13/14
Stimulus target	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Stimulus type	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Pulse waveform	✓	x	✓	✓	✓	✓	x	✓	✓	x	✓	x	✓	x	9/14
Paired-pulse interval	N.A.	N.A.	N.A.	N.A.	N.A.	✓	N.A.	✓	N.A.	✓	N.A.	N.A.	N.A.	✓	4/4
Inter-trial interval	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14
Number of trials per averaged response[b]	✓	✓	x	x	✓	x	x	✓	✓	✓	✓	✓	✓	✓	10/14
TMS-EMG acquisition	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14/14

TABLE 3 (Continued)

	Valentin et al. (2008)	Del Felice et al. (2011)	Julkunen et al. (2013)	Shafi et al. (2015)	Ter Braack et al. (2016)	Kimiskidis et al. (2017)	Bauer et al. (2019)	Premoli, Castellanos, et al. (2014)	Premoli, Biondi, et al. (2017)	Premoli et al. (2018)	Darmani et al. (2019)	Premoli et al. (2019)	Belardinelli et al. (2021)	Ruijs et al. (2022)	Proportion of reporting studies
EEG protocol															
Filtering	x	✓	x	✓	x	✓	x	x	x	x	✓	x	✓	x	5/14
Electrode reference	x	✓	✓	✓	✓	x	x	x	x	x	✓	x	x	x	5/14
Electrode type	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0/14
Sampling rate	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	12/14

Note: Only the first of the articles describing studies with identical study populations and TMS interventions is mentioned. ✓ = reported. x = not reported.

Abbreviations: EEG, electroencephalography; EMG, electromyography; N.A., not applicable; TMS, transcranial magnetic stimulation.

[a]Not applicable to the orientation of circular TMS coils positioned over the vertex.

[b]Represented by grand averages per study group or study condition.

different between people with epilepsy and controls, but the number of studies was low (N100: 3/4 studies, P180: 3/3 studies). The directions of the effects were conflicting. TMS-related spectral perturbations of gamma power were altered in people with epilepsy compared to controls in all studies. The direction of effect, however, was not uniform between studies, and their numbers were limited.

4 | DISCUSSION

Current evidence for TMS-evoked EEG responses as epilepsy or anti-seizure medication biomarkers is inadequate. We found poor reporting of epilepsy population parameters and a lack of uniformity of TMS-EEG protocols between studies. Establishing the added value of TMS-EEG registrations in the diagnostic work-up of epilepsy and monitoring of anti-seizure medication effects requires standardised methodology, reporting and more studies to strengthen the evidence.

Study population characteristics were variably reported, the least mentioned being comorbidities, MRI findings and seizure types in epilepsy. Comorbidities are common in epilepsy (Keezer et al., 2016), and some are believed to affect cortical excitability independent of epilepsy. For example, depression, which occurs in half of the people with epilepsy (Kanner, 2003), has been associated with diminished cortical inhibition, though this seems primarily the case in younger individuals (Lewis et al., 2016; Lissemore et al., 2018). Other central nervous system comorbidities, such as intellectual disability and migraine – particularly among those with auras – may also impact cortical excitability (Bauer et al., 2021; Chronicle et al., 2006). These examples stress the relevance of reporting comorbidities in individuals who participate in TMS-EEG studies. Seizure types may differentially impact measures of cortical excitability with marked postictal contrasts between focal to bilateral tonic–clonic and focal impaired awareness seizures (Helling et al., 2022). Thus, it is essential to report seizure types and the interval between the most recent seizure and TMS measurement. MRI findings may be abnormal in non-focal epilepsies, those in which classification is unknown, and individuals diagnosed with focal epilepsy (Woermann et al., 1998). Hence, reporting such clinical data is essential for interpreting measures of cortical excitability as these may deviate in those with structural abnormalities in the targeted area (Liepert et al., 2005).

Conversely, we found overall higher reporting rates for TMS-EEG methodological parameters, though with striking differences between TMS and EEG protocols. The least mentioned TMS protocol parameter was the timing of the TMS evaluations. The influence of clock time alone on within-subject TEP variability seems negligible (Ter Braack et al., 2019). Citing the TMS schedule, however, is essential since this may suggest the potential impact of any processes fluctuating throughout the day, such as the degree of alertness (Ferrarelli et al., 2010; Noreika et al., 2020), on the TMS-evoked EEG responses. Regarding EEG parameters, none of the studies reported on the use of active or passive electrodes, and fewer than half of the studies depicted online filtering and electrode reference practices. Electrode type presumably does not impact the spatiotemporal TEP distribution

TABLE 4 Values per selected transcranial magnetic stimulation (TMS)-EEG protocol parameter for all studies.

Parameter	Values	Number of studies	% of total
TMS sessions and equipment			
Stimulator type	Magstim (Model) 200 or 200[2]	7	50
	MagVenture MagPro X100	2	14
	Magstim Rapid[2]	2	14
	Nexstim eXimia	2	14
	MagVenture MagPro R30	1	7
Coil type	Butterfly/Fig-8	12	86
	Circular	2	14
Coil diameter	90 mm	8	57
	70 mm	2	14
	140 mm	1	7
	Not reported	*3*	*21*
Coil positioning	Frame-stabilized/manual	8	57
	Neuronavigation	4	29
	Not reported	*2*	*14*
Coil-induced current direction	Posterior-to-anterior (fig-8)	4	29
	Anterior-to-posterior (fig-8)	1	7
	Custom orientation per subject (fig-8)	1	7
	Clockwise and counter-clockwise (circular)	1	7
	Not reported	*7*	*50*
Coil click sound masking	Active (i.e. ear-/headphones with noise)	9	64
	Passive (i.e. foam earplugs)	3	21
	Combination of active and passive	1	7
	Not reported	*1*	*7*
TMS trials			
Stimulus intensity	MT-based	12	86
	Not MT-based	1	7
	Not reported	*1*	*7*
Stimulus target	M1 (motor hotspot)	10	71
	Cz	2	14
	All 10–20 EEG positions	1	7
	Subject-specific (PNH-related)	1	7
Stimulus type	SP only	10	71
	Both PP and SP	4	29
Pulse waveform	Monophasic	6	43
	Biphasic	3	21
	Not reported	*5*	*36*
Number of trials per averaged response	≥80	7	50
	<80	3	21
	Not reported	*4*	*29*
TMS-EMG acquisition	rMT	13	93
	MEP amplitude	3	21
	SICI	3	21
	aMT	1	7
	LICI	1	7
	SI1mV	1	7
	Not performed	1	7

TABLE 4 (Continued)

Parameter	Values	Number of studies	% of total
EEG protocol			
Electrode reference	Common	4	29
	Average	1	7
	Not reported	*9*	*64*
Electrode type	Active	0	0
	Passive	0	0
	Not reported	*14*	*100*

Note: Only the first of the articles describing studies on identical study populations and with identical TMS interventions is considered.
Abbreviations: (a/r)MT, (active/resting) motor threshold; EEG, electroencephalography; EMG, electromyography; fig-8, figure-of-eight; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; PNH, periventricular nodular heterotopia; PP, paired-pulse; SI1mV, stimulation intensity to evoke motor evoked potentials of 1 millivolt; SICI, short-interval intracortical inhibition; SP, single-pulse; TMS, transcranial magnetic stimulation.

or discharge artefact interference (Freche et al., 2018; Mancuso et al., 2021). Yet, active electrodes may be less suited to track rapid voltage alternations (Laszlo et al., 2014), substantiating the report of this parameter, especially regarding TIO analyses in the higher frequency domain. While analogue EEG filters, due to their wide ranges, typically do not distort the TEP or TIO, reporting filter cut-offs is warranted in order to comprehend the likelihood and extent of filter artefact injection into the signals (Acunzo et al., 2012; Tanner et al., 2015). Likewise, mentioning the online EEG reference is essential since both the choice for an average or common electrode reference, and latter's location, may significantly influence artefact behaviour (Freche et al., 2018; Mutanen et al., 2022).

We found marked heterogeneity between study protocol parameters, some of which are critical for interpreting the TMS-EEG response. Accurate coil positioning, for example, is essential in serial experiments and when using coils generating focal magnetic fields as minor deviations may impact the TMS-evoked EEG responses (de Goede et al., 2018). Fewer than half of the studies employed coil positioning with neuronavigation. Active masking of the TMS coil click may prevent the contamination of the TEP by the AEP (ter Braack et al., 2015). Yet, close to a quarter of the studies that disclosed the use of masking employed earplugs without masking noise. The use of mono- or biphasic pulse waveforms is a choice that may depend on interest in particular response characteristics such as early or late TEP components (Pisoni et al., 2018). Pulse waveform has also been associated with the global TMS-evoked response magnitude (Casula et al., 2018), underlining the need for adequate reporting of this parameter. The mean number of TMS trials included per subject-averaged response affects the repeatability of the TMS-EEG response (Kerwin et al., 2018). Nearly half of the studies used at least 80 trials, but the remainder either included less than 80 trials or failed to report this parameter.

Comparability of outcomes across studies is further challenged by the impact of additional secondary (somato)sensory inputs and EEG artefacts – physiological and non-physiological – on TMS-evoked EEG responses (Conde et al., 2019; Rogasch et al., 2013). This reflects an urgent need for standardised and robust methods to minimise the risk of artefactual responses (Belardinelli et al., 2019). Real-time optimisation of the signal-to-noise ratio before acquisition of the response trials is a recent methodological advance towards standardised acquisition practices (Casarotto et al., 2022).

We did not identify a consistent pattern for the reported effects of anti-seizure medication on TMS-evoked EEG responses. This may be explained by the distinct pharmacodynamic profiles underlying the anti-seizure medications under investigation. We neither found consistent profiles when comparing TMS-EEG responses in people with epilepsy to controls. Various aetiologies may have driven such a result in epilepsy. Other explanations for these results include the small number of studies and the heterogeneity across study protocols. The effects of anti-seizure medications, for example, appear to depend on the adjustment of post-intervention stimulus intensity to an altered rMT (Premoli, Costantini, et al., 2017). Lastly, the intrinsic variability of cortical responses to TMS could have impacted the uniformity of TMS-evoked EEG response outcomes across studies. Averaged TMS-evoked EEG responses appear highly reproducible within subjects (Kerwin et al., 2018; Lioumis et al., 2009), but between-subject variability of cortical excitability points towards intrinsically heterogenous TMS-EEG responses across individuals (Chagas et al., 2018). Therefore, possible use scenarios would favour TMS-EEG to study within-individual effects, such as of initiating new pharmacological treatment for people with epilepsy in therapeutic response evaluation or elucidating neuromodulatory mechanisms using pharmaco-TMS-EEG in drug development. Regarding the latter, accumulating evidence for the ability of TMS to reveal oscillatory EEG changes following anti-seizure medication administration potentially opens additional avenues towards widespread employment in pharmaceutical trials (Belardinelli et al., 2021)–(Tangwiriyasakul et al., 2019). Nevertheless, adequate control for individual traits that could steer TMS-EEG responses, for example the phase of ongoing oscillations (Baur et al., 2020), may permit clinical applications across individuals, such as in the diagnostic work-up.

We appraised the quality of reporting by evaluating many study cohort and TMS-EEG protocol parameters, partly based on a Delphi consensus study (Chipchase et al., 2012). Assessed TMS-EEG protocol parameters included items describing the administration of the magnetic pulses rather than the analysis of the evoked responses. We

TABLE 5 Effects of anti-seizure medication on transcranial magnetic stimulation (TMS)-evoked EEG responses reported by studies on healthy individuals.

Article	TMS-evoked EEG response	Therapeutic intervention (dose)	Post-intervention vs. baseline or placebo effect per response parameters									
			N15/ P25/P30	N45	P60/70	N100	P180	δ	θ	α	β	γ
Effects probed by sp-TMS												
Premoli et al. (2014)[a]	TEP	APZ (1 mg)	n.s.	↑	n.s.	↓	n.s.	–	–	–	–	–
		DZP (20 mg)	n.s.	↑	n.s.	↓	n.s.	–	–	–	–	–
Premoli, Biondi, et al. (2017)[a]	TEP	LTG (300 mg)	n.s.	↑	n.s.	n.s.	↓	–	–	–	–	–
		LVT (3000 mg)	n.s.	↑	n.s.	↓	↓	–	–	–	–	–
Premoli, Constantini, et al. (2017)[a]	TEP	LTG (300 mg)	n.s.	n.s.	n.s.	n.s.	↓	–	–	–	–	–
		LVT (3000 mg)	n.s.	↑	↓	n.s.	n.s.	–	–	–	–	–
Premoli, Bergmann, et al. (2017)[a]	TIO	APZ (1 mg)	–	–	–	–	–	–	–	n.s.	↓	–
		DZP (20 mg)	–	–	–	–	–	–	–	↑	↓	–
Premoli et al. (2018)	TEP	DZP (20 mg)	n.s.	↑	n.s.	↓	↓	–	–	–	–	–
Darmani et al. (2019)	TEP	BRV (100 mg)	n.s.	n.s.	n.s.	↓	n.s.	–	–	–	–	–
		CBZ (600 mg)	↓	↑[b]	n.s.	n.s.	↓	–	–	–	–	–
		TGB (15 mg)	n.s.	n.s.	n.s.	n.s.	n.s.	–	–	–	–	–
Premoli et al. (2019)[a]	TEP	XEN1101 (20 mg)	↓	↓	n.s.	↓	↓	–	–	–	–	–
Tangwiriyasakul et al. (2019)[a]	TIO	LTG (300 mg)	–	–	–	–	–	–	n.s.	↓	n.s.	–
		LVT (3000 mg)	–	–	–	–	–	–	n.s.	↓	n.s.	–
Belardinelli et al. (2021)	TEP	PER (6 or 12 mg)	n.s.	n.s.	↓	n.s.	n.s.	-	-	-	-	–
	TIO	PER (6 or 12 mg)	–	–	–	–	–	–	–	↑	↑	n.s.
Biondi et al. (2022)[a]	TIO	LTG (300 mg)	–	–	–	–	–	↓	↓	↑	n.s.	n.s.
		LVT (3000 mg)	–	–	–	–	–	n.s.	↓	↓	↓	n.s.
		XEN1101 (20 mg)	–	–	–	–	–	↓	↓	↓	↓	n.s.
Ruijs et al. (2022)	TEP	LOR (2 mg)	n.s.	n.s.	n.s.	n.s.	n.s.	–	–	–	–	–
		LVT (2000 mg)	n.s.	↑	n.s.	↓	n.s.	–	–	–	–	–
		VPA (100 mg)	n.s.	n.s.	n.s.	n.s.	n.s.	–	–	–	–	–
Number of reports per effect (sp-TMS)												
			n.s.: 13 ↓: 2	↑: 8 n.s.: 6 ↓: 1	n.s.: 13 ↓: 2	n.s.: 8 ↓: 7	n.s.: 9 ↓: 6	↓: 2 n.s.: 1	↓: 3 n.s.: 2	↓: 4 ↑: 3 n.s.: 1	↓: 4 n.s.: 3 ↑: 1	n.s.: 4

TABLE 5 (Continued)

Article	TMS-evoked EEG response	Therapeutic intervention (dose)	Post-intervention vs. baseline or placebo effect per response parameters									
			N15/ P25/P30	N45	P60/70	N100	P180	δ	θ	α	β	γ
Effects probed by pp-TMS												
Premoli, Rivolta, et al. (2014)[a]	TEP	DZP (20 mg)	n.s.	n.s.	n.s.	↓	↓	–	–	–	–	–
Premoli et al. (2018)	TEP	DZP (20 mg)	n.s.	n.s.	n.s.	↓	n.s.	–	–	–	–	–
Ruijs et al. (2022)	TEP	LOR (2 mg)	n.s.	n.s.	n.s.	↓	n.s.	–	–	–	–	–
		LVT (2000 mg)	n.s.	↑	↑	↓	[c]	–	–	–	–	–
		VPA (100 mg)	↑	n.s.	n.s.	n.s.	n.s.	–	–	–	–	–
Number of reports per effect (pp-TMS)												
			n.s.: 4 ↑: 1	n.s.: 4 ↑: 1	n.s.: 4 ↑: 1	↓: 4 n.s.: 1	n.s.: 3 ↓: 1 [c]: 1	–	–	–	–	–

Note: Response parameters of TMS-evoked EEG potentials are indicated by a 'P' or 'N' (i.e. positive or negative deflection, respectively) combined with the post-stimulus latency in milliseconds. Parameters of TMS-induced oscillations, that is power per EEG frequency band, are represented by Greek symbols (δ = delta, θ = theta, α = alpha, β = beta, and γ = gamma). ↑ = increased TEP component amplitude or oscillatory power (sp-TMS)/intracortical inhibition (pp-TMS). ↓ = decreased TEP component amplitude or oscillatory power (sp-TMS)/intracortical inhibition (pp-TMS). – = not investigated.
Abbreviations: APZ, alprazolam; BRV, brivaracetam; CBZ, carbamazepine; DZP, diazepam; EEG, electroencephalography; LOR, lorazepam; LTG, lamotrigine; LVT, levetiracetam; N.A., not applicable; n.s., non-significant; PER, perampanel; pp-TMS, paired-pulse TMS; sp-TMS, single-pulse TMS; TEP, TMS-evoked EEG potential; TIO, TMS-induced oscillation; TGB, tiagabine; TMS, transcranial magnetic stimulation; VPA, valproic acid.
[a]Overlapping cohorts and TMS procedures.
[b]For the stimulation intensity not adjusted to the post-intervention resting motor threshold.
[c]Significant difference (direction not detailed).

TABLE 6 Effects of subject type (people with epilepsy vs. healthy controls) on transcranial magnetic stimulation (TMS)-evoked EEG responses reported by case–control studies.

			Effect of the subject group (people with epilepsy vs. healthy controls) on response parameters										
Article	**TMS-evoked EEG response**	**Epilepsy type**	**N15/P25/P30**	**N45**	**P60/70**	**N100**	**P180**	**δ**	**θ**	**α**	**β**	**γ**	**Remaining findings**
Effects probed by sp-TMS													
Valentin et al. (2008)	0–1 s post-TMS interval	FE	–	–	–	–	–	–	–	–	–	–	Amplitude and morphologic differences 0–1 s post-TMS
Del Felice et al. (2011)	TEP	GE	n.s.	n.s.	n.s.	↑	↑	–	–	–	–	–	–
Julkunen et al. (2013)	TEP	GE	↑	–	–	↓	↓	–	–	–	–	–	↑ GFP 15-25 ms post-TMS[a] ↓ GFP 55-95 ms and 150-175 ms post-TMS[a]
	TIO		–	–	–	–	–	–	–	↓	↓	↓	–
Shafi et al. (2015)	TEP	FE	–	–	–	–	–	–	–	–	–	–	↑ AUC-GFP 225–400 ms and 400–700 ms post-TMS
Ter Braack et al. (2016)	TEP	GE, FE	n.s.	n.s.	n.s.	↑	↑	–	–	–	–	–	–
Kimiskidis et al. (2017)	TEP	GE	n.s.	–	n.s.	n.s.	–	–	–	–	–	–	Feature sets classifying study groups[c]
Bauer et al. (2019)	TEP	GE	–	–	–	–	–	–	–	–	–	–	Amplitude differences 55-63 ms post-TMS[a,b]
	TIO		–	–	–	–	–	–	–	n.s.	n.s.	↑[b]	–
Vlachos et al. (2022)	TIO	GE	–	–	–	–	–	n.s.	n.s.	n.s.	n.s.	↑	–
Number of reports per effect (sp-TMS)													
			n.s.: 3 ↑: 1	n.s.: 2	n.s.: 3	↑: 2 ↓: 1 n.s.: 1	↑: 2 ↓: 1	n.s.: 1	n.s.: 1	n.s.: 2 ↓: 1	n.s.: 2 ↓: 1	↑: 2 ↓: 1	
Effects probed by pp-TMS													
	TEP	GE	n.s.	–	n.s.	n.s.	–	–	–	–	–	–	Feature sets classifying study groups[c]
Number of reports per effect (pp-TMS)													
			n.s.: 1	–	n.s.: 1	n.s.: 1	–	–	–	–	–	–	

Note: Response parameters of TMS-evoked EEG potentials are indicated by a 'P' or 'N' (i.e. positive or negative deflection, respectively) combined with the post-stimulus latency in milliseconds. Parameters of TMS-induced oscillations, that is power per EEG frequency band, are represented by Greek symbols (δ = delta, θ = theta, α = alpha, β = beta, and γ = gamma). ↑ = increased TEP component amplitude, GFP, oscillatory power, or inter-trial phase clustering (sp-TMS)/intracortical inhibition (pp-TMS). ↓ = decreased TEP component amplitude, GFP, oscillatory power or inter-trial phase clustering (sp-TMS)/intracortical inhibition (pp-TMS). – = not investigated.

Abbreviations: EEG, electroencephalography; FE, focal epilepsy; GE, generalised epilepsy; (AUC-)GFP, (area under the curve of the) global field power; n.s., non-significant; pp-TMS, paired-pulse TMS; sp-TMS, single-pulse TMS; TEP, TMS-evoked EEG potential; TIO, TMS-induced oscillation; TMS, transcranial magnetic stimulation.

[a]Inferred from figure.

[b]Medication-naïve people with epilepsy only.

[c]Classifier for the differentiation between people with GE and healthy controls appeared discriminatory using sp-TMS P60 and N100 amplitudes during rest (accuracy level 0.86) and hyperventilation (accuracy level 0.81), and sp-TMS P60 amplitude and N30-P60 amplitude difference post-hyperventilation (accuracy level 0.92). Classifier for the differentiation between people with epilepsy responding to anti-seizure medications vs. non-responders and healthy controls appeared discriminatory using derivatives of TEP delta band energy profiles during rest (accuracy level 0.80); pp-TMS P60-100 area during hyperventilation (accuracy level 0.78); and sp-TMS N30-P60 amplitude difference and P60-100 area, and pp-TMS P60 amplitude and N100 latency post-hyperventilation (accuracy level 0.65).

acknowledge the influence of pre-processing and analysis methodology on the TMS-EEG readout (Bertazzoli et al., 2021), but these items were outside the scope of this review. Our assessment of the reporting of methodological parameters was distorted because multiple studies were conducted with the same subject cohorts and experimental set-ups. We accounted for this by only using the first article in our analysis of reported study parameters.

5 | CONCLUSION

There is a pressing need to standardise protocols and reporting to explore the potential of TMS-evoked EEG measures as a proxy for cortical excitability in epilepsy. This is especially relevant for parameters that critically affect the interpretation of study findings, for example appropriate coil positioning to ensure target consistency. These improvements would aid the critical appraisal of TMS-evoked EEG responses as biomarkers for disease and treatment-induced effects on seizure propensity (Belardinelli et al., 2019; Julkunen et al., 2022; Tremblay et al., 2019).

AUTHOR CONTRIBUTIONS

Silvano R. Gefferie, Josemir W. Sander, Simona Balestrini, and Roland D. Thijs conceptualised and designed the study. Data was collected and curated by Silvano R. Gefferie, Diego Jiménez-Jiménez, Simona Balestrini and Roland D. Thijs. The initial manuscript was drafted by Silvano R. Gefferie, and edited by Josemir W. Sander, Simona Balestrini and Roland D. Thijs. All authors reviewed and approved the final version.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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