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Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG

Sung Wook Chung [a], Nigel C. Rogasch [b], Kate E. Hoy [a], Paul B. Fitzgerald [a,*]

[a] Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Australia
[b] Brain and Mental Health Laboratory, School of Psychological Sciences and Monash Biomedical Imaging, Monash University, Melbourne, Australia

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ABSTRACT

Neuromodulatory brain stimulation can induce plastic reorganization of cortical circuits that persist beyond the period of stimulation. Most of our current knowledge about the physiological properties has been derived from the motor cortex. The integration of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) is a valuable method for directly probing excitability, connectivity and oscillatory dynamics of regions throughout the brain. Offering in depth measurement of cortical reactivity, TMS-EEG allows the evaluation of TMS-evoked components that may act as a marker for cortical excitation and inhibition. A growing body of research is using concurrent TMS and EEG (TMS-EEG) to explore the effects of different neuromodulatory techniques such as repetitive TMS and transcranial direct current stimulation on cortical function, particularly in non-motor regions. In this review, we outline studies examining TMS-evoked potentials and oscillations before and after, or during a single session of brain stimulation. Investigating these studies will aid in our understanding of mechanisms involved in the modulation of excitability and inhibition by neuroplasticity following different stimulation paradigms.

Introduction

Neuromodulatory brain stimulation can induce plastic reorganization of cortical circuits which persist beyond the period of stimulation [1]. A variety of neuromodulation techniques are currently used to modulate brain activity, the most common of which are repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). Traditionally measuring the cortical effect of these techniques has been restricted to the motor cortex, namely due to the easily measureable output of motor evoked potentials (MEPs) which occurs in response to single and paired pulse TMS. As such there is a large body of existing work which has used this non-repetitive TMS over the motor cortex to track changes in cortical activity resulting from neuromodulatory brain stimulation paradigms, specifically looking at corticomotor excitability and cortical inhibition [2–5]. To expand the brain regions and range of variables that can be measured before and after neuromodulation, researchers have increasingly combined this single and paired pulse TMS with electroencephalogram (EEG). Concurrent use of TMS and EEG (TMS-EEG) allows a method for probing varied superficial cortical brain regions to study intracortical neural circuits [6]. Furthermore, TMS-EEG captures additional cortical properties such as the generation of oscillatory brain activity and the propagation of signals to other cortical regions [7]. In this review, we summarize the impact of the most commonly applied neuromodulatory techniques on motor cortical excitability determined using MEPs. We then examine the cortical properties that can be assessed using TMS-EEG and explore how these measures compliment and extend information gained from MEPs. Finally, we outline the studies that have used this approach to assess changes in cortical properties resulting from neuromodulatory paradigms in both motor and non-motor regions, particularly looking at TMS-evoked potentials (TEPs) and oscillations before and after, or during one single session of brain stimulation.

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* Corresponding author. Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Road, Melbourne, Victoria 3004, Australia. Tel.: +61 3 9076 6552; fax: +61 3 9076 8545.
E-mail address: paul.fitzgerald@monash.edu (P.B. Fitzgerald).

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Effects of neuromodulatory brain stimulation on brain function

Neuromodulatory paradigms can influence neural activity in humans in different ways, either increasing or decreasing cortical excitability depending on the stimulation parameters [8–11]. This unique ability to safely modulate cortical activity has led to many experimental and therapeutic applications using these techniques. However, inter-individual variability and state-dependency of neuromodulatory brain stimulation approaches need to be taken into account when efficacy and reliability of these paradigms are investigated [12]. In this section, we briefly overview the effects of four of the main neuromodulatory brain stimulation paradigms on corticomotor excitability derived from motor cortex studies using MEPs as the outcome measure.

rTMS

TMS can be used either to measure cortical properties, including excitation and inhibition, or temporarily alter the organization of cortical circuits [13]. When TMS is given repetitively, it has been shown to have a neuromodulatory effect. Repetitive TMS involves delivery of repeated single pulse stimulation to a specific brain region [14], and has been shown to alter cortical excitability that outlasts the period of the stimulation [9]. Depending on the frequency of stimulation, the after-effects can either increase or decrease cortical excitability [15]. However, these outcomes can vary between subjects, and can be affected by the initial activation state of the targeted neural population [16]. Despite intra- and interindividual variability of responses to rTMS [17], low-frequency rTMS ($\sim$1 Hz) has been shown to reduce cortical excitability, while high-frequency rTMS (5–20 Hz) has shown to increase excitability [18]. Believed to mimic the effects of long-term potentiation (LTP) and long-term depression (LTD), rTMS has been used both to study plasticity and as a therapeutic tool in various neurological and psychiatric disorders [19–22].

TBS

Theta burst stimulation (TBS) is a modified form of rTMS, involving pulses applied in bursts of three at 50 Hz with an inter-burst interval at 5 Hz [8]. Two different paradigms of TBS are commonly used; continuous TBS (cTBS), and intermittent TBS (iTBS). Briefly, cTBS involves either 300 or 600 pulses of uninterrupted TBS delivery, and has shown to reduce cortical excitability for up to 60 min. Intermittent TBS comprises of 2 s of TBS trains repeated every 10 s, with a total number of 600 pulses applied, and has shown to increase cortical excitability for at least 15 min [8]. Even though relatively reproducible effects of iTBS [23] and cTBS [24] have been described, variable effects between subjects have also been demonstrated [25]. Nevertheless, due to shorter duration of stimulation (1–3 min) and lower intensity used compared to conventional rTMS, TBS may prove to be more effective way of modifying brain activity. TBS has been employed with therapeutic intent, but widespread use of clinical use of TBS is yet to emerge [26].

PAS

Paired associative stimulation (PAS) protocols consist of pairing of electrical stimulation of median nerve and cortical TMS over the contralateral motor cortex (M1) [11]. Effects resembling spike-time dependent plasticity (STDP), LTD-like or LTP-like plasticity of corticospinal neurons are observed depending on the interstimulus interval (ISI) of the paired stimulation [27]. PAS with ISI of 10 ms has shown to reduce cortical excitability, and ISI of 25 ms has shown to increase cortical excitability [28]. Bidirectional Hebbian-like plasticity has also been displayed between interconnected cortical areas [29,30]. Similar to other neuromodulatory paradigms, inter-individual variability and age-dependency of PAS have been described [31].

tDCS

Plastic reorganization can also be induced by passing a small current across the scalp, a brain stimulation method known as transcranial direct current stimulation. The underlying mechanisms resulting in changes from tDCS are different to that of TMS. Unlike TMS, tDCS modulates the likelihood of neural firing by changing neuronal membrane potentials [32]. tDCS involves delivery of a weak current (1 or 2 mA) to the scalp with a pair of electrodes, inducing subthreshold modulation of resting membrane potential [33]. Depending on the polarity of the current flow, stimulation intensity and duration, tDCS can lead to increase or decrease in cortical excitability [34]. Anodal tDCS, which involves placing the anode over the stimulation target and the cathode to a reference site, has shown to increase cortical excitability under the anode. On the other hand, cathodal tDCS employs the opposite arrangement to the anodal tDCS, and has shown to reduce cortical excitability at the site of cathodal stimulation [35]. tDCS is attracting considerable research attention as a technique for potentially improving aspects of cognition such as learning, memory, attention and decision-making [37–41]. In addition, tDCS has demonstrated potential therapeutic effects in neurological [42,43] and psychiatric conditions [44,45]. However, a recent meta-analysis has reported that tDCS does not produce reliable changes in many of these measures (with the exception of MEP sizes), bringing into question the general efficacy of the technique [36]. Therefore, further studies directly assessing the neural and behavioral effects of tDCS in non-motor regions are required.

Combining TMS and EEG to measure cortical properties

Despite the wealth of information gained from motor cortex studies on neuromodulatory brain stimulation, recordings of TMS-induced physiological effects (e.g. muscle twitch and MEPs) have not traditionally been accessible in non-motor cortical regions. In brain regions other than motor cortex, other measurable effects such as the perception of phosphenes with TMS [46] and behavioral outcome (task performance) have been investigated although these effects can be limited by either subjectivity or variable effects. A growing body of research is now exploring the after-effects of different neuromodulation techniques by recording EEG concurrently to TMS [29,47–49].

EEG is a commonly-used technique which measures the electrical activity of neurones and allows for non-invasive measurement of spontaneous and event-related brain activity from the entire surface of the brain [50]. Electrophysiological responses induced by a single pulse TMS can be illustrated with waveforms and topographic representation of TMS-evoked potentials (TEPs), providing a direct measure of brain activity [51]. This measure is cortical in nature and not influenced by non-cortical confounds such as spinal cord excitability, which can limit MEP-based measures of cortical excitability. In addition to being able to look at TEPs in non-motor brain regions, the combination of TMS with EEG also allows for more detailed assessment of cortical activity, specifically 1) cortical excitation/inhibition balance by measuring TEPs, 2) cortical connectivity by analyzing that spatiotemporal propagation of activity following TMS and 3) the intrinsic ability of the stimulated region to generate oscillatory activity (Fig. 1).

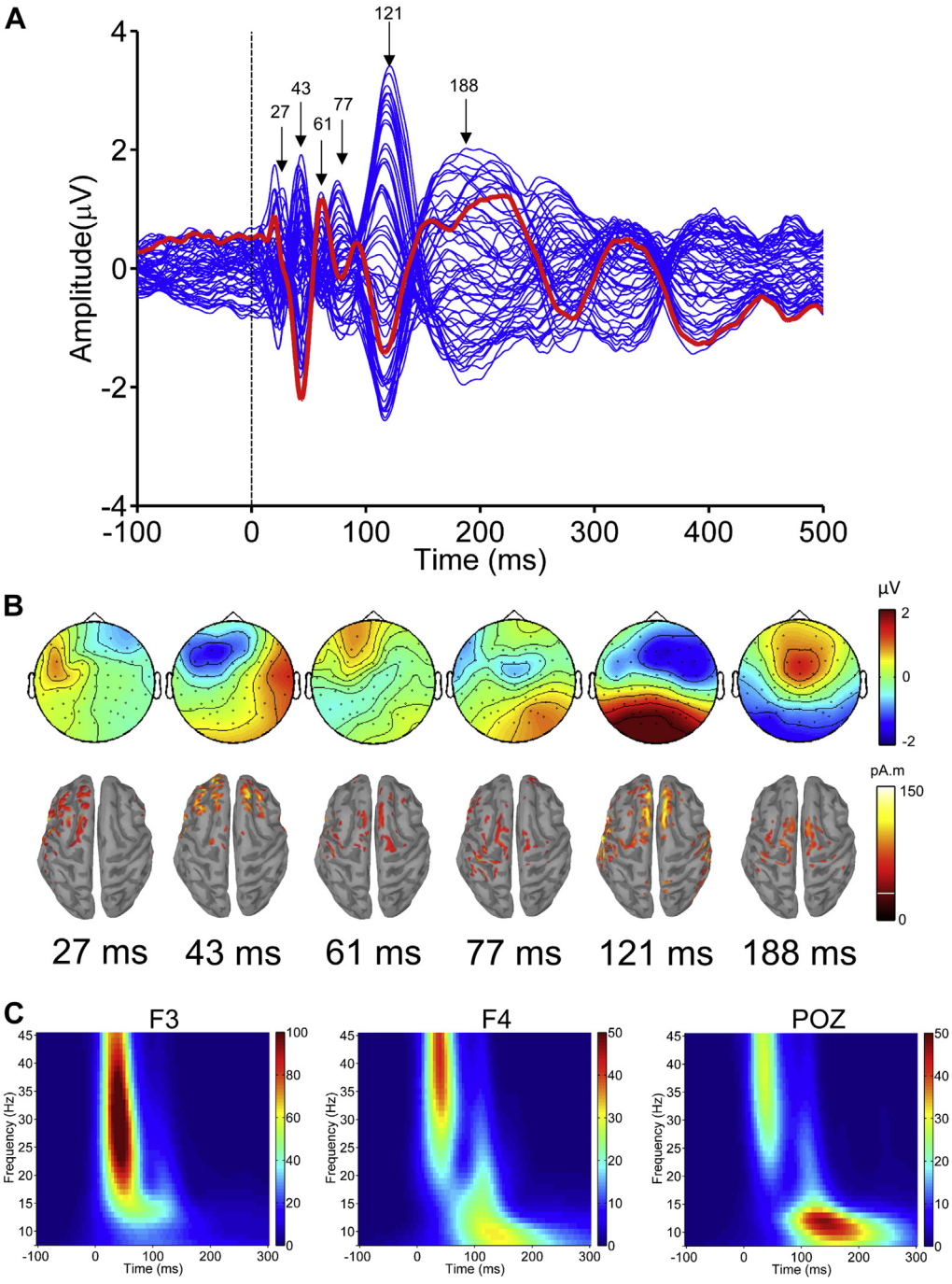

Figure 1. TMS-evoked cortical activity following stimulation of the left dorsolateral prefrontal cortex. A) TMS-evoked potentials from all electrodes averaged across 30 participants. The red line represents the electrode under the coil. B) TMS-evoked cortical connectivity measured by assessing the spatiotemporal propogation of activity following TMS both on the scalp (upper topoplots) and following source reconstruction (bottom plots). C) TMS-evoked oscillatory activity measured from three different electrodes. (Adapted from NeuroImage, 1(101), Rogasch et al., Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties, 425-39, Copyright (2014), with permission from Elsevier.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

TMS-evoked potentials

TEPs represent shifts in the inhibition-excitation balance in cortical circuits following a single TMS pulse [52]. Several studies have shown that TEPs are highly reproducible over time and are sensitive to changes in stimulation parameters such as intensity, location, coil angle and current direction [29,53–59]. TEPs following stimulation of the motor cortex consist of a series of negative and positive deflections lasting up to 300 ms, and these peaks are usually defined as N15, P30, N45, P55, N100, P180 and N280 [60]. Studies have suggested that early peaks reflect excitatory activity due to a positive correlation between peak-to-peak amplitude of N15–P30 component and MEP amplitude [61–63], and that N15–P30 amplitude varies depending on the angle of the TMS coil [53]. Premoli and colleagues (2014) [64] demonstrated that the generation of N45 potential is mediated by activation of

gamma-aminobutryic acid (GABA)–A receptor, and N100 potential by GABA-B activity. Initially, N100 and P180 were believed to be associated with coil click sound [62]. Studies using sound masking protocol (e.g. white noise) have found that cortical activation by TMS contribute to the change in amplitude of N100–P180 complex [65–67]. Several studies have now identified the N100 component to be linked to cortical inhibitory processes [62,63,65,68–70]. Peaks with similar latencies have also been observed from non-motor regions. The physiological origin and functional significance of peaks from non-motor regions are yet to be fully elucidated, although the N100 over prefrontal cortex is also consistent with GABA-B mediated inhibition [70,71]. Modulation of short-latency potentials (P5 and P8) have recently been described to evaluate the reactivity of the stimulated cortex [72,73], but is still in debate as these peaks possibly reflect muscle artifacts [74,75].

TMS-evoked connectivity

Analyzing the latencies and cortical distribution of TEPs, either on the scalp or by using source localization can be used to infer the propagation of activity from the site of stimulation to anatomically connected regions [53,76]. Ipsilateral spreading via association fibers and contralateral propagation through transcallosal and subcortical pathways have been described in various studies [6,56,62,77,78], allowing the investigation of cortico-cortical and cortico-subcortical interactions. A recent diffusion tensor imaging study supported transcallosally mediated TMS-induced inter-hemispheric signal propagation, suggesting that the corpus callosum is involved in the spreading of cortical potentials, and the level of activation is dependent on the intensity of TMS [79].

TMS-evoked oscillations

TMS-evoked responses can also be examined in the frequency domain, revealing information on the intrinsic ability of the stimulated region to generate or entrain oscillations in discrete frequency bands [49,80–84]. Such synchronous activity of neurons in specific rhythms are fundamental for neuronal network communication and information processing [85]. The oscillatory patterns are categorized into bands of frequencies based on the physiological properties, ranging from delta to gamma (delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–70 Hz)) [86]. Delta-band oscillations are prominent in sleep [87], and are linked to motivational drive [88,89]. Theta waves are associated with memory processes [90], and alpha waves are involved in cognitive inhibition [91]. In early studies, alpha-band oscillations were believed to originate from idle brain regions [92]. However, recent studies have proposed alpha to reflect functional inhibition via event-related synchronization, instead of neural inactivity [91,93,94]. Beta-band oscillations are prominent during normal state of wakefulness with open eyes, and are associated with motor control [95,96]. Lastly, gamma-band oscillations are involved in a variety of behavioral components, such as working-memory [97], visual perception [98] and attention [99]. Reduced gamma oscillations have been described in the frontal cortex in schizophrenia patients using TMS-EEG [100,101].

Single-pulse TMS over motor cortex can lead to a brief period of synchronization in beta bands which are thought to reflect a phase-resetting of ongoing oscillations which are amplified by the thalamus [81,84]. In addition, natural frequency preservation of each cortical area has been demonstrated. Stimulation of different cortical regions results in oscillations at different frequencies – alpha-band oscillations (8–12 Hz) in the occipital cortex, beta-band oscillations (13–20 Hz) in the parietal cortex, and fast beta/gamma-band oscillations (21–50 Hz) in the frontal cortex [82], which may provide a guideline to explore the physiological mechanisms involved in generation of oscillations. Therefore, concurrent use of TMS and EEG offers dynamic measures of brain responses and functionality both in healthy and pathological conditions.

Probing brain stimulation-induced changes in cortical properties using TMS-EEG

As described above, TMS-EEG provides additional information on cortical properties than studies of only motor cortex output. Cortical reactivity can also be explored in depth by investigating changes in latency, amplitude, distribution and waveforms of TEPs, which can act as quantifiable markers in a similar manner to MEPs, allowing study of cortical properties outside of the motor cortex. The plasticity inducing properties of non-invasive brain stimulation allows temporary modification of cortical activity in a targeted brain region, which then can be propagated to induce remote or global changes in excitability [102–104]. Different measures are used in different studies and indexes of global and local cortical excitability can be determined by examining: (1) local TEPs with peaks measured from single electrodes, (2) global TEPs with peaks measured using Global Mean Field Power (GMFP) analysis, and (3) TMS-evoked oscillations. To date, a limited number of studies have looked at the excitability changes following neuromodulatory paradigms using TMS-EEG, with rTMS studied the most.

Effects of rTMS using TMS-EEG

Investigation of the direct effects of neuromodulation on cortical excitability using TMS-EEG can be approached using two methods; (1) off-line method with single pulse TMS-EEG recorded before and after neuromodulation to examine the short-term and long-term after-effects, and (2), on-line method with EEG recorded during modulation to examine the on-going TMS-evoked changes. Below we review studies of both off-line and on-line methods for low frequency and high frequency rTMS. The reviewed studies are further summarized in Table 1.

Effects of low frequency rTMS

Recently, Casula and colleagues (2014) [105] showed a site-specific modulation in excitability using single pulse TMS-EEG measured only from M1 when 1 Hz rTMS was applied on both M1 and primary visual cortex (V1). Increases in the amplitude of the P60 and N100 TEPs was seen with M1 stimulation but not V1, and sustained increase in the late local TEPs was more pronounced in the same hemisphere [105], suggesting that 1 Hz rTMS increases inhibitory drive.

Helfrich and colleagues (2012) [47] reported what appears to be a contradictory finding in children with attention deficit hyperactivity disorder (ADHD), observing a reduction in the TMS-evoked N100 amplitude following 1 Hz rTMS over M1. On-line analysis during the study showed a more pronounced decrease in N100 amplitude during the first half of 900 rTMS pulses, and demonstrated a saturation effect of rTMS on cortical excitability [47]. There may be a limit to pulses applied for maximal excitability change at a given time, and an exploration of optimal parameters would allow for more systemic assessment and comparison. A limitation of this study was having no active auditory masking (i.e. white noise) as such auditory evoked potentials may have masked the N100 TEP [67,106,107]. However, reduction in amplitude of N100 has been illustrated in other recent TMS-EEG studies on children with ADHD compared to healthy individuals [108,109], with this finding possibly reflecting the pathophysiology of the illness. In conjunction with direct evidence linking N100 component to GABA-B

Table 1
TMS-EEG measuring neural plasticity pre/post (off-line) and during (on-line) rTMS.

Neuro-modulation	Authors	Subjects	Stimulation parameters	EEG recording	Measurement (examined TEPs)	After effects
rTMS (LF-rTMS)	Van Der Werf and Paus (2006) [84]	$N = 12$ Mean age: 29.4 Healthy	M1 (left) & Dorsal Premotor Cortex (Left) 0.6 Hz, 90% rMT, 560 pulses (15 min)	M1 (left) spTMS (Pre & Post rTMS at 0, 10, 20 & 30 min) ISI: 4–6 s 115% rMT, 50 pulses 8 scalp channels Auditory masking: white noise (80 dB)	Global TEPs (P30, N45, N100, P200) TMS-evoked oscillations	↓ N45 following M1 rTMS but NOT PMC stimulation – Reduction at 0 min before returning to baseline (10 min), and increasing (20 & 30 min) ↓ amplitude of theta oscillation after both M1 and PMC conditioning
	Brignani et al. (2008) [80]	$N = 6$ Mean age: 34 Healthy	M1 (left) 1 Hz, 110% rMT, 600 pulses (10 min)	On-line (During rTMS) 19 scalp channels Auditory masking: Earplugs	TMS-evoked oscillations	↑ power synchronization in the alpha band from 1st to 3rd block of stimulation, and inversely correlated with MEPs amplitude. 1st block: 1–200 pulses 2nd block: 201–400 pulses 3rd block: 401–600 pulses
	Helfrich et al. (2012) [47]	$N = 25$ Mean age: 11.0 ADHD	M1 (left) 1 Hz, 80% rMT, 900 pulses (15 min)	On-line (During rTMS) & M1 (left) spTMS (Pre & Post rTMS) ISI: 6–10 s 110% rMT, 20 pulses 64 scalp channels Auditory masking: Hearing protection	Local TEPs (N100)	↓ N100 amplitude following rTMS (more pronounced decrease during the first half) but not with sham
	Veniero et al. (2012) [73]	$N = 13$ Age: 18–30 Healthy	M1 (left) & PMC (left) 1 Hz, 70% rMT, 900 pulses (3 × 300 pulses with 1 min interval)	M1 (left) spTMS (Pre & Post rTMS) ISI: 1.4–5 s 110% rMT, 200 pulses 70 scalp channels Auditory masking: earplugs	Local TEPs (P5, N8)	Group analysis showed no significance. ↓ amplitude of P5 & N8 in 6 participants, ↑ in 2 participants after PMC conditioning (but not M1 conditioning) ↓ P5 & N8 amplitude showed ↑ MEPs ↑ P5 & N8 amplitude showed ↓ MEPs
	Casula et al. (2014) [105]	$N = 15$ Mean age: 25 Healthy	M1 (left) and V1 (left) 1 Hz, 90% rMT, 1200 pulses (20 min)	M1 (left) spTMS (Pre & Post rTMS) ISI: 4–6 s 120% rMT, 50 pulses 31 scalp channels Auditory masking: white noise (~90 dB)	Local TEPs (P30, N45, P60, N100, P180)	↑ amplitude of P60 & N100 after M1 conditioning (but not V1 conditioning) Sustained ↑ in the late TEPs, especially in the stimulated hemisphere
rTMS (HF-rTMS)	Esser et al. (2006) [113]	$N = 7$ Mean age: 26 Healthy	M1 (left) 5 Hz, 90% rMT, 1500 pulses (50 pulses in 10 s burst, 6 bursts a train with 5 s interval, 5 trains in total with 60 s interval)	M1 (left) spTMS (Pre & Post rTMS) ISI: 0.5–0.7 s 90% rMT, 200 pulses 60 scalp channels Auditory masking: white noise (~90 dB)	Global TEPs (~5, ~18, ~35, ~55, ~84 ms)	↑ EEG response following rTMS – Significant at 2nd (~18 ms), 3rd (~35 ms) and 4th (~55 ms) peak in premotor cortex, bilaterally.
	Veniero et al. (2010) [72]	$N = 16$ Mean age: 23.4 Healthy	M1 (left) 20 Hz, 100% rMT, 400 pulses (10 pulses per train, 40 trains total with 14.55 s inter-train interval)	On-line (During rTMS) 29 scalp channels Auditory masking: white noise (~90 dB)	Local TEPs (P5, N8, P30, N45)	↑ amplitude and ↓ latency in early TMS-evoked responses (P5 & N8), but no significant change in P30 or N45
	Hamidi et al. (2010) [114]	$N = 16$ Mean age: 22.5 Healthy	SPL (left) & PCG (left) 10 Hz, 110% rMT, 2880 pulses (30 pulses per train with minimum of 17.1 s inter-train interval)	On-line (During rTMS) 60 scalp channels Auditory masking: white noise	Global TEPs (~4, ~26, ~42, ~60, ~84 ms)	A series of 5 evoked brain potentials occurring at approximately 4, 26, 42, 60 & 84 ms after each TMS pulse Except for the 1st peak, amplitude of TMS-evoked response ↓ and ↑ during a train (quadratic relationship), at both SPL and PCG.

ADHD – Attention deficit hyperactivity disorder; EEG – Electroencephalogram; ISI – Interstimulus interval; LF/HF – Low/high frequency; M1 – Primary motor cortex; MEPs – Motor evoked potentials; PCG – Postcentral gyrus; PMC – Premotor area; rMT – Resting motor threshold; rTMS – Repetitive transcranial magnetic stimulation; SPL – Superior parietal lobule; spTMS – Single-pulse TMS; TEPs – TMS-evoked potentials; V1 – Primary visual cortex.

mediated inhibition [63,64,70], TMS-evoked N100 may be a reliable marker for cortical inhibition.

Another on-line study by Brignani and colleagues (2008) [80] showed that 1 Hz rTMS on M1 increased even-related alpha and beta synchronization, preferentially in the stimulated hemisphere. The modulation in alpha oscillations increased with duration of stimulation and was inversely correlated with MEPs amplitude [80], possibly reflecting another marker for cortical inhibition using TMS-EEG. It is worth noting that alpha oscillations (~10 Hz) and the N100 (peak at 100 ms – i.e. one 10 Hz cycle) may reflect similar mechanisms.

With respect to off-line studies, Van Der Werf and Paus (2006) [84] applied 0.6 Hz rTMS over both primary motor cortex (M1) and dorsal premotor cortex (PMC) in separate sessions, and recorded changes in cortical excitability following rTMS using single-pulse TMS-EEG over M1. There was a decrease in the N45 component of TMS-evoked response immediately after M1 rTMS and returned to baseline 10-min post stimulation [84]. No change in M1 was observed after PMC conditioning, demonstrating a site-specific TMS-EEG response, even though other rTMS studies stimulating PMC showed changes in M1 excitability [110–112]. M1 and PMC rTMS resulted in the reduction of theta oscillation amplitudes in this study, which was regarded as an auditory habituation to the click of single-pulse TMS. Despite TMS-EEG studies in deaf showing the presence of an N100 component [66,67], modulation of N100 was interpreted as an auditory neural response to the TMS coil click [84]. This, together with using different stimulation frequency (0.6 Hz) may explain the discrepancy in results from the study done by Casula and colleagues (2014) [105].

Veniero and colleagues (2012) [73] examined the modulation in short-latency TMS-evoked potentials using single-pulse TMS-EEG over M1 before and after 1 Hz rTMS was applied on both M1 and PMC in separate sessions, but no statistically significant differences in the amplitudes of both MEPs and TEPs were observed with either type of stimulation. However, single subject analysis showed a reduction in peak-to-peak amplitude of the P5-N8 complex after PMC conditioning, which was negatively correlated with MEP amplitude changes [73]. Even though these early TEP components may be informative for cortical excitability changes, one should be cautious on interpreting the results, as P5-N8 complex has been shown to largely reflect muscular activation [74,75].

Effects of high frequency rTMS

Esser and colleagues (2006) [113] recorded single-pulse TMS-EEG before and after the application of high frequency 5 Hz rTMS to left M1. Source localization revealed predominant activation in premotor cortex which suggests that connections between M1 and premotor cortex were strengthened. Global TEPs showed significant increase in TMS-evoked responses following 5 Hz rTMS compared to sham, except for the first peak (~5 ms) and the last peak (~84 ms) [113]. It was suggested that first peak primarily corresponded to motor cortical activity where no potentiation was observed, and late component may result from different sources than the earlier components [113]. Similar results were seen with Hamidi and colleagues (2010) [114], when 10 Hz rTMS was applied to both superior parietal lobule (SPL) and postcentral gyrus (PCG) while EEG was recorded simultaneously. This on-line analysis showed amplitude changes in both stimulated area in TMS-evoked peaks (4, 26, 42, 60, and 94 ms post-pulse) with exception to the first peak in global field power [114]. Another on-line study using 20 Hz rTMS by Veniero and colleagues (2010) [72] reported a contradictory finding, showing increased amplitudes in early peaks (P5 & N8) of TMS-evoked response, but not in the later peaks (P30 & N45). This is particularly interesting because high-frequency rTMS paradigms induce cortical potentiation, but different frequencies result in different on-line effects on TEPs. The two paradigms might result in a similar cumulative effect on cortical excitability through different interacting mechanisms. However, given insufficient number of studies, it is too early to speculate on the exact mechanism or specific neuronal populations that are involved in eliciting cortical excitability using different frequency, and further studies are required to contrast different stimulation protocols.

Effects of other modulatory techniques using TMS-EEG

There are only a few studies exploring the effects of other neuromodulation techniques using TMS-EEG, and this makes direct comparison problematic. More studies of this nature would allow for more systemic analysis of temporal variation and spatial distribution of TMS-evoked responses and aid in better understanding of physiological changes with different modulation paradigms. We review the research that has been conducted below, with the studies further summarized in Table 2.

PAS

Huber and colleagues (2008) [115] demonstrated changes in amplitude of global TEPs following two different forms of PAS on M1 that correlated with MEPs. PAS ISI 10 ms showed significant change at 75 ms post-pulse, and PAS ISI 25 ms at 70, 84, 139 and 168 ms post-pulse. The authors noted that the correlation was weak and MEPs may not be considered the only indicator of cortical excitability change [115]. Similar to interindividual variability seen in MEPs amplitude, TMS-evoked responses measured using EEG also showed variability after PAS. However, PAS resulted in both local and contralateral changes in the amplitude of TMS-evoked responses that indicated change in sensorimotor excitability [115].

Rajji and colleagues (2013) [116] recently showed PAS-induced potentiation of cortical-evoked activity on Dorsolateral Prefrontal Cortex (DLPFC), which was site and frequency specific. Frequency-specific potentiation of cortical excitability was demonstrated within gamma, theta as well as delta frequency bands, but not within the alpha and beta bands. Modulation of theta and gamma coupling shown in this study suggested PAS-induced potentiation produces synaptic effect and may have an impact on a wide range of cognitive functions [116].

Veniero and colleagues (2013) [29] showed increased connectivity in alpha and beta bands between posterior parietal cortex (PPC) and M1 following cortico-cortical PAS. Three different PAS methods with 5 ms interval were used in separate sessions: (1) PPC following M1, (2) PPC preceding M1, and (3) PPC following M1 (with different coil angle). Single-pulse TMS-EEG was recorded before and after each stimulation at both sites. Spread of activation was more evident after M1 stimulation, including contralateral site, and lack of PPC response to PAS was postulated to be affected by insufficient stimulation intensity and target-dependent modulation [29]. Nonetheless, global TEPs amplitude revealed modulation of M1 reactivity, particularly in peak 1 (~20 ms) and peak 4 (~175 ms), and the ability to selectively manipulate the functional connectivity between two cortical regions was demonstrated [29].

TBS

To date, only one study has investigated the effect of TBS using concurrent TMS-EEG. Vernet and colleagues (2013) [49] used a slightly modified cTBS protocol from the original paradigm and applied this to the motor cortex. Inhibition of P30 TEPs was observed, which was closely related to the changes in MEPs, and low variance to individual TEPs was discussed. A combination of the

Table 2
TMS-EEG measuring neural plasticity pre/post (off-line) and during (on-line) other modulation techniques.

Neuro-modulation	Authors	Subjects	Stimulation parameters	EEG recording	Measurement (examined TEPs)	After effects
PAS	Huber et al. (2008) [115]	$N = 19$ Mean age: 25.2 Healthy	90 stimuli of right median nerve at the wrist (0.5 ms) M1 (left) 130% rMT, every 15 s ISI: 10 ms & 25 ms (22.5 min)	M1 (left) spTMS (Pre & Post PAS) ISI: 0.5–0.7 s 90% rMT, 200 pulses 60 scalp channels Auditory masking: Noise masking	Global TEPs (~32, ~74, ~138, ~170 ms)	Distinct peaks with similar latencies (~32, ~74 & ~170 ms): ↑ amplitude after PAS ISI 25 ms ↓ amplitude after PAS ISI 10 ms Local and contralateral site
	Rajji et al. (2013) [116]	$N = 15$ Age: 18–50 Healthy	180 stimuli of right median nerve DLPFC (left) Intensity needed for MEP amplitude of 1 mV (SI_{1mv}), every 10 s ISI: 25 ms (15 subjects) & 100 ms (9 control subjects) (30 min)	DLPFC (left) spTMS (Pre & Post PAS at 0, 15 & 30 min) ISI: 10 s SI_{1mv}, 100 pulses 64 scalp channels	– TMS-evoked oscillations	↑ cortical-evoked activity after PAS (25 ms) at the target site and across left frontal area, but not contralaterally or globally Potentiation within gamma, theta & delta, but not in alpha or beta frequency bands.
	Veniero et al. (2013) [29]	$N = 13$ Mean age: 27.6 Healthy	100 pairs of stimuli 1. PPC → $M1_{(P\text{-}A)}$ (left) 2. $M1_{(P\text{-}A)}$ → PPC (left) 3. PPC → $M1_{(A\text{-}P)}$ (left) 90% rMT, every 5 s (~8.3 min) ISI: 5 ms	M1 (left) & PPC (left) spTMS (Pre & Post PAS) ISI: ~4 s SI_{1mv} (~130% rMT), 80 pulses 20 scalp channels Auditory masking: earplugs	Global TEPs (~18, ~53, ~108, ~186 ms) TMS-evoked oscillations	1. PPC → $M1_{(P\text{-}A)}$: ↑ amplitude of Peak 1 (~18 ms) with ↓ MEPs after stimulating M1, but not PPC 2. $M1_{(P\text{-}A)}$ → PPC: ↓ amplitude of Peak 1 & Peak 4 (~186 ms) with ↑ MEPs after stimulating M1, but not PPC 3. PPC → $M1_{(A\text{-}P)}$: ↓ amplitude of Peak 1 & Peak 4 with ↑ MEPs after stimulating M1, but not PPC ↑ alpha-band coherence with ↑ MEPs ↑ beta band coherence with ↓ MEPs
TBS	Vernet et al. (2013) [49]	$N = 10$ Mean age: 21 Healthy	M1 (left) cTBS – 3 bursts of pulses at 50 Hz every 240 ms (4.17 Hz) 80% aMT, 600 pulses	M1 (left) spTMS (Pre & Post TBS at 0, 5, 10, 20, 30, 40, 50 & 60 min) ISI: 5–8 s 120% rMT, 10–30 pulses 60 scalp channels Auditory masking: Earplugs	Local TEPs (P30, N45, P55, N100) TMS-evoked oscillations	↓ amplitude of P30 with ↓ MEPs ↓ alpha & theta oscillation ↑ beta oscillation
tDCS	Pellicciari et al. (2013) [35]	$N = 16$ Mean age: 23.2 Healthy	Anodal & Cathodal tDCS Intensity of 1 mA, 13 min Size: 25 cm^2 Current density: 0.04 mA/cm^2 Active: M1 Reference: right frontopolar cortex 8 s fade-in/fade-out	M1 (left) spTMS (Pre & Post tDCS at 0 & 30 min) ISI: 2–4 s 110% rMT, 100 pulses 14 scalp channels Auditory masking: earplugs	Local TEPs (16–40 ms, 59–105 ms, 182–264 ms) Oscillations	Anodal tDCS – ↑ cortical-evoked activity over both hemisphere Left (↑): 0 min: 20–27 ms, 51–72 ms & 258–265 ms 30 min: 15–33 ms & 54–75 ms Right (↑): 0 min: 10–16 ms, 86–96 ms & 209–231 ms 30 min: 86–96 ms & 205–233 ms Cathodal tDCS – ↓ cortical-evoked activity over stimulated hemisphere,↑ over contralateral Left (↓): 0 min: 206–238 ms 30 min: 201–217 ms Right (↑): 0 min: 37–41 ms & 124–152 ms 30 min: 34–39 ms, 124–131 ms ↑ theta & alpha power after anodal and cathodal tDCS

(*continued on next page*)

Table 2 (*continued*)

Neuro-modulation	Authors	Subjects	Stimulation parameters	EEG recording	Measurement (examined TEPs)	After effects
	Romero Lauro et al. (2014) [48]	$N = 14$ Mean age: 27 Healthy	Anodal tDCS & Sham Intensity of 0.75 mA, 15 min Anode (right PPC): Size: 9 cm^2 Current density: 0.08 mA/cm^2 Cathode (left supraorbital): Size: 25 cm^2 Current density: 0.03 mA/cm^2 8 s fade-in/fade-out For sham tDCS, stimulator turned off after 30 s	PPC (left) spTMS (During, Pre & Post tDCS at 15 min) ISI: 2–2.3 s 60–78 % rMT, ~180 pulses 60 scalp channels Auditory masking: Noise masking	Global TEPs (0–50 ms, 50–100 ms, 100–150 ms) Local TEPs (0–50 ms, 50–100 ms, 100–150 ms)	↑ cortical reactivity at 0–100 ms both during and after 15 min anodal tDCS ↑ cortical reactivity at 0–50 ms in the right PPC, contralateral area & bilateral frontal regions after 15 min anodal tDCS

A-P – Anterior-posterior; DLPFC – Dorsolateral prefrontal cortex; ISI – Interstimulus interval; M1 – Primary motor cortex; MEPs – Motor evoked potentials; P-A – Posterior-anterior; PAS – Paired associative stimulation; PPC – Posterior parietal cortex; rMT – Resting motor threshold; spTMS – Single-pulse TMS; cTBS – Continuous theta burst stimulation; tDCS – Transcranial direct current stimulation; TEPs – TMS-evoked potentials.

different TEPs appeared to be the main factor predicting amplitude of MEPs, and more studies are required to clarify the observation to the individual level [49]. Additionally, the pattern of TMS-induced oscillations was modified, with decrease in low-frequencies (theta and alpha) and increase in high-frequency (high beta) followed by cTBS [49]. With more TMS-EEG studies, TEPs and oscillations could provide important information about the plasticity in the brain regions other than motor cortex.

tDCS

Pellicciari and colleagues (2013) [35] measured cortical reactivity using TMS-EEG following anodal and cathodal tDCS and found polarity-dependent and site-specific modulation of neuronal activity induced by TMS. The anodal tDCS induced an increase in cortical-evoked activity in both hemispheres, while the cathodal tDCS induced a decrease in stimulated but not in non-stimulated hemisphere (see Table 2). However, both stimulation paradigms showed general increase in theta and alpha power. It was suggested that these cortical responses to the TMS could be physiological markers for cortical excitability, with TEPs being more sensitive than the EEG power density [35]. Supporting this study, Romero and colleagues (2014) [48] studied the effects of anodal tDCS to right posterior parietal cortex (PPC) and observed a shift in cortical excitability within ipsilateral and contralateral hemispheres. Earlier components of TEPs (~50 ms) were significantly modulated shown by both global TEPs and local TEPs which reflect the excitability of stimulated and interconnected areas [48].

Conclusion

TMS-EEG studies of different neuromodulatory techniques have shown that there are distinctive changes in TEPs before and after brain stimulation. In particularly, peaks occurring approximately at 30 ms, 45 ms and 100 ms following motor cortex stimulation seem more frequently affected by neuromodulation, and change in alpha and theta frequencies are most prevalent in the studies investigated. Even though peaks occurring at different time points and changes in various frequency bands have been illustrated, until more studies of this nature are conducted, it is too early to pinpoint the origin of the TEPs induced by different stimulation techniques. In particular, it is important to note that TEPs from different brain regions can have different latencies, topographies and amplitudes [55], and may reflect different underlying neurophysiological mechanisms. Therefore, judgments about the capacity to generalize the effect of stimulation techniques on TEP components to inform studies in the motor cortex to other brain regions needs further investigation. Additionally, the heterogeneity in stimulation parameters, EEG recording and signal processing methods, as well as strategy of each study in controlling confounds needs to be considered for a more systematic comparison.

TMS-EEG offers a highly sensitive measurement of cortical activity from both the stimulated region and connected, but remote cortical areas. In particular, TMS-EEG enables the evaluation of TEPs that may act as a marker for cortical excitation and inhibition, and provides valuable information from cortical areas not traditionally assessed using TMS. Recording neuronal responses in the millisecond time frame, the dynamics of neural connections can be mapped to investigate functional interactions in the human brain. In addition, TMS-evoked oscillations allow examination of brain oscillatory activity to help clarify the mechanisms involved in processing and transfer of information between brain areas. However, the physiological origin and functional significance of some of the TMS-evoked components

remain to be defined. With carefully designed experimental approaches, many of technical challenges of TMS-EEG can be overcome, and exploring the modification of cortical activity by different neuromodulatory techniques can contribute to unraveling the mechanisms involved in modulation of excitability and inhibition by neuroplasticity, both in healthy and neuropsychiatric population.

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