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Review

Clinical utility and prospective of TMS–EEG

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HIGHLIGHTS

- An overview of TMS-EEG methodology and neurophysiological derivations.
- A comprehensive review of TMS-EEG as a clinical tool to study healthy and disease brain states.
- A discussion of current challenges in the field of TMS-EEG and recommendations for future studies.

ABSTRACT

Concurrent transcranial magnetic stimulation and electroencephalography (TMS–EEG) has emerged as a powerful tool to non-invasively probe brain circuits in humans, allowing for the assessment of several cortical properties such as excitability and connectivity. Over the past decade, this technique has been applied to various clinical populations, enabling the characterization and development of potential TMS–EEG predictors and markers of treatments and of the pathophysiology of brain disorders. The objective of this article is to present a comprehensive review of studies that have used TMS–EEG in clinical populations and to discuss potential clinical applications. To provide a technical and theoretical framework, we first give an overview of TMS–EEG methodology and discuss the current state of knowledge regarding the use of TMS–EEG to assess excitability, inhibition, plasticity and connectivity following neuromodulatory techniques in the healthy brain. We then review the insights afforded by TMS–EEG into the

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pathophysiology and predictors of treatment response in psychiatric and neurological conditions, before presenting recommendations for how to address some of the salient challenges faced in clinical TMS–EEG research. Finally, we conclude by presenting future directions in line with the tremendous potential of TMS–EEG as a clinical tool.

Contents

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method used to probe neurophysiological processes within the brain (Hallett, 2007). Over the last 30 years, TMS has been widely used to study clinical populations in search of a better understanding of the underlying pathophysiology of various disorders. However, until recently, the generalization, application and clinical translation of findings have been hindered by the fact that TMS was mostly limited to the study of motor areas of the brain (Ilmoniemi and Kičić, 2010; Thut and Pascual-Leone, 2010; Daskalakis et al., 2012). The combination of TMS and electroencephalography (EEG) has permitted experiments designed to non-invasively examine brain states (Massimini et al., 2009b) and their dynamics across motor and non-motor cortical areas (Pellicciari et al., 2017b), including the examination of cortico-cortical interactions on a millisecond time-scale (Bortoletto et al., 2015), of normal and abnormal plasticity mechanisms (Chung et al., 2015), as well as of interactions between excitatory and inhibitory mechanisms (Barr et al., 2013). Hence, TMS–EEG greatly expands the scope of neurophysiological information that can be derived from studies using TMS combined with electromyography (EMG) and enables probing brain function across almost all areas of the cortical mantle and associated cortical networks – making it a highly powerful emerging tool to study clinical populations.

The objective of this review is to provide a comprehensive overview of TMS–EEG as (1) a method for studying neurophysiological markers of healthy brain function, and (2) a possible diagnostic and prognostic tool among clinical populations. We will first present the methodology of TMS and EEG, and provide a summary of the neurophysiological properties of the cortex that can be derived from TMS–EEG, as well as the current methods for analysis of TMS-related artifacts. We will then review TMS–EEG studies that have been conducted in healthy volunteers. We will focus specifically on studies assessing cortical inhibition and excitation, connectivity, pharmacology of TMS–EEG, and the ability to measure plasticity in cortical circuits following neuromodulatory brain stimulation, to provide a background for TMS-EEG applications in patients. This will lead to a comprehensive review of studies that have employed TMS–EEG in clinical populations and a discussion of the potential clinical applications of the technique. Finally, we will discuss future directions in the field TMS–EEG and its potential for translation to clinical practice.

2. TMS–EEG principles and methodology

2.1. Co-registration of TMS and EEG

TMS involves the generation of brief time-varying magnetic fields that, through the principle of electromagnetic conduction, induce an electric field (E-field) in a nearby conductor, i.e. the human brain when applied over the head. The E-field generated in the cortex by TMS depolarizes neurons resulting in a brief period of synchronized neural firing in the area underlying the TMS coil. When applied over the motor cortex, suprathreshold TMS pulses can either directly or trans-synaptically depolarize corticospinal neurons, which results in the activation of muscles in the periphery innervated by the stimulated cortical region. These TMS-evoked muscle activations, known as motor-evoked potentials (MEPs), can be recorded using electromyography (EMG), and the amplitude of MEPs provides an index of corticospinal excitability. Although extremely useful in measuring cortical properties such as excitation/inhibition, plasticity and connectivity, there are two major limitations of the TMS–EMG experimental design. First, TMS–EMG paradigms are restricted to the motor system and cannot be easily translated to non-motor regions due to their dependence on motor output. Second, the MEP is not only influenced by cortical mechanisms, but also spinal excitability and muscle properties. To overcome these limitations, TMS has been combined with neuroimaging techniques, which more directly measure brain activity, such as EEG.

When a TMS pulse is applied to the cortex, time-locked depolarization of underlying neurons is obtained, as well as trans-synaptic activation of local and distal cortical networks. This activity can be recorded through the skull by EEG electrodes placed on the scalp: where the summation of synaptic potentials produces a series of positive and negative deflections visible in the EEG signal, termed the TMS-evoked potential (TEP). Mirroring the principles of MEPs, the TEP is a measure of cortical reactivity; changes in its amplitude and latency reflect changes in cortical activity of the stimulated region.

The first demonstration of a co-registration of TMS and EEG was conducted by Cracco and colleagues in 1989 (Cracco et al., 1989). A few years later, Ilmoniemi et al. (1997) employed this multimodal approach to circumvent the fact that imaging methods, such as functional magnetic resonance imaging (fMRI), did not allow for the sensitive temporal assessment of cortico-cortical connections and direct cortical reactivity. They showed that cortical activity induced by a TMS pulse can be recorded starting from a few milliseconds after stimulation of either motor or occipital cortices, and that this activity spreads to the homologue cortical areas of the contralateral hemisphere around 20 ms later (Ilmoniemi et al., 1997). As such, they were able to demonstrate, for the first time, that TMS combined with high-resolution EEG allows for measuring the initial response to the TMS pulse, but also to quantify and characterize spread of activation that follows in time, spatial and frequency domains (Ilmoniemi et al., 1997). Since these early experiments, TMS–EEG has matured into its own subfield with numerous laboratories around the world now undertaking TMS–EEG research. Please refer to Farzan and colleagues (Farzan et al., 2016) for a comprehensive description of the methodology for TMS–EEG protocols.

2.2. Origin of TMS-EEG responses

Although the precise origin of TEPs remains to be determined, they are thought to involve the spatial and temporal summation of excitatory and inhibitory post-synaptic potentials originating from the activity of a large population of cortical pyramidal neurons and interneurons (Kirschstein and Köhling, 2009; Hill et al., 2016; Luck and Kappenman, 2017). Animal studies exploring the neural elements activated by TMS can provide insights into the probable origin of cortical signals. For example, single neuron recordings in non-human primates following suprathreshold TMS have shown that the TMS pulse activates pyramidal neurons, as well as non-pyramidal neurons and neuronal elements such as putative axons (Mueller et al., 2014). This activation was shown to last more than 200 ms at the population level, which corresponds to the duration of the TEP. There is also evidence from in vitro studies that suggest that TMS can activate specific cortical microcircuits such as axons in layer 5 that synapse onto GABAB-mediated neurons in layer 1 (Murphy et al., 2016), supporting the assumption that TMS-EEG can be an index of GABAergic activity. TMS has also been coupled with EEG in animal models of epilepsy, demonstrating the possibility to use the same methodology as in humans allowing for translational studies (Rotenberg et al., 2008). Biophysical models of TMS can also provide important information on the source of evoked brain signals recorded via EEG. Studies suggesting that individual brain anatomy, coil orientation and coil location greatly influence the induced current in the brain provide a framework to understand the variations in the TEP waveform recorded in different scalp loca-

tion, as described in Section 4, and could help define targets for future TMS-EEG studies (see (Goetz and Deng, 2017) for review). Additionally, the extensive literature on describing the neurophysiology of somatosensory evoked potentials (SEP) and somatosensory evoked oscillations supports the notion that different aspects of the EEG signal can reflect differential cortical processes probed by an external output (Macerollo et al., 2018). Altogether, these studies provide a framework to understand the cortical properties of the EEG activity recorded following the TMS pulse, suggesting that the TMS-evoked EEG signal may reflect different levels of cortical activation.

3. Artifacts in TMS–EEG signals

3.1. TMS–EEG artifacts

The main challenge in the concurrent application of TMS and EEG was related to the very large artifact that is produced by the electromagnetic field generated by the TMS coil, which is several orders of magnitude larger than electrophysiological activity of the brain recorded by the EEG, and initially resulted in saturation of EEG amplifiers (Ilmoniemi et al., 1997). The first TMS–EEG technique employed to prevent this artifact consisted in a sample-and-hold circuit, where the electrode is decoupled from the amplifier shortly before the TMS pulse, allowing for EEG recordings as early as 2 ms following the pulse (Ilmoniemi et al., 1997; Virtanen et al., 1999). In recent years, the introduction of direct current (DC) coupled amplifiers, as opposed to previous alternating current (AC) amplifiers, allows for the prolonged negative deflection caused by the TMS pulse to immediately return to a linear range after stimulation (Daskalakis et al., 2012). The recent development of EEG amplifiers with high sampling rates (e.g., > 5 kHz) provide the opportunity for a detailed and complete characterization of the TMS artifact, which can be removed offline during post-hoc analyses techniques (Daskalakis et al., 2012). Furthermore, the development of TMS-compatible EEG electrodes also allowed for minimization of artifacts.

Common artifacts in TMS–EEG recordings arise from several sources, which are discussed in depth in recent reviews (Ilmoniemi and Kičić, 2010; Rogasch and Fitzgerald, 2013; Ilmoniemi et al., 2015; Farzan et al., 2016). Typically, they include common EEG artifacts, such as environmental noise (e.g., power-line) and physiological noise (e.g., cardiac rhythms, eye blinks, head movements, activity from facial/scalp muscles), as well as TMS-related artifacts, which arise from various sources. When stimulating a specific region, the coil is inevitably in contact with the electrodes surrounding the target region. Stimulation can thus produce movements of EEG sensors due to the electromagnetic field and coil vibration. The pressure of the coil on the electrodes can also produce artifacts in the signal. Moreover, the magnetic field applied on the electrode, the electrode-skin interface, as well as the capacitor recharge in TMS stimulators will also contribute to the production of artifacts in the signal. Altogether, these factors underline to the so-called TMS-induced decay artifact (Veniero et al., 2009; Sekiguchi et al., 2011), which is a large positive shift in the signal that linearly recovers within up to 50 ms. However, using TMS-compatible recordings along with proper measures to avoid artifacts and off-line artifacts correction, the decay artifact can recover within 10–12 ms allowing to measure early latency TMS-evoked potential (Litvak et al., 2007; Rogasch et al., 2013b). Briefly, for reduction of artifacts, the use of EEG electrodes designed for TMS applications is highly recommended (Veniero et al., 2009). An appropriate skin preparation and low signal impedance (Julkunen et al., 2008b), the addition of a thin piece of foam under the coil to reduce direct contact with electrodes (Massimini et al., 2005) and the re-orientation of electrode wires perpendicular to the stimulating coil (Sekiguchi et al., 2011) can also help minimize the TMS-decay artifacts.

There are also some confounding factors secondary to the TMS pulse that should be reduced by adopting specific strategies. Firstly, the TMS pulse results in a loud clicking noise (100–120 dB), which can cause an auditory-evoked potential. Importantly, this evoked-potential is typically observed at the same latency as the N100/P190 complex, which can mask the "real" TMS-induced potential (Nikouline et al., 1999). Wearing sound protective headphones and/or playing white noise in earphones is typically used to maximally reduce this artifact (Paus et al., 2001; Fuggetta et al., 2005; Ferrarelli et al., 2010; ter Braack et al., 2015). Secondly, the TMS pulse may also activate sensory afferents, resulting in a tapping sensation on the scalp that can induce a somatosensory-evoked potential. The use of a thin layer of foam under the coil may help attenuating this effect.

Thirdly, the TMS pulse can produce facial muscle activation and time-locked blinks induced by the TMS pulse. These artifacts are especially observed during frontal or lateral stimulation (Mutanen et al., 2013). Such artifacts are typically suppressed with off-line analyses that will be described below, although it is difficult to ascertain how well neural activity is preserved following these suppression methods. When studying global brain responses to perturbation, without a specific interest on a well-defined circuit, stimulating cortical regions close to the midline might help reducing unwanted activation of scalp muscles by TMS. Overall, the potential contribution of the effects of multisensory stimulation on TEP waveforms has been recently confirmed by Conde and collaborators (Conde et al., 2018) employing a sham condition.

A viable strategy to reduce the relative contribution of sensory confounding factors is to maximize the impact of stimulation by making sure that TMS elicits strong initial cortical responses at the stimulation site. For example, studies aimed at assessing global changes in thalamocortical complexity across brain states (Ferrarelli et al., 2010; Sarasso et al., 2015) elicited initial responses during wakefulness that were up to one order of magnitude larger than the ones reported in Conde and collaborators (Conde et al., 2018). Using this approach, TEPs are specific for the stimulation parameters (site, intensity, orientation) and are characterized by even larger responses upon loss of consciousness, unlike SEPs. Most important, specific changes across states in the time-frequency features (Rosanova et al., 2009; Fecchio et al., 2017) and overall complexity of the responses to TMS both at early and late latency (Massimini et al., 2005), can be replicated by intracranial electrical stimulation (Pigorini et al., 2015; Comolatti et al., 2018), which does not elicit any sensory percept. Eliciting prominent cortical responses to TMS clearly depends not only on stimulation intensity but also on several other factors ranging from coil orientation and design, to the extent and morphology of the impacted cortex. Thus, in order to ascertain the amplitude of early TEP components, it would be important to develop and apply real-time standardized data visualization tools during the experimental procedures.

While this strategy can be viable when exploring changes in global brain states, the use of a sham condition may be useful to control for sensory-related confounding factors (Daskalakis et al., 2008; Gordon et al., 2018a) in experiments where TMS is aimed at exploring subtle changes occurring in specific, local circuits. In practice, sham condition has been recently implemented by either stimulating the shoulder (Herring et al., 2015) or by a more accurate reproduction of TMS sensory input by means of concurrent electrical stimulation of the scalp combined with the TMS click (Conde et al., 2018; Gordon et al., 2018a) titrated on subjective reports and psychophysics. This can be used to elicit the multisen-

sory component that can be eventually subtracted to recover the genuine cortical activation induced by TMS. However, developing such sham condition may be challenging in the clinical practice if patients are non-collaborating or practically unfeasible in the case of unresponsive patients.

3.2. Offline procedures for artifact removal

Apart from technical improvements that can limit artifacts during recording, offline processing procedures for artifact removal have also contributed to the development and the growing use of TMS–EEG. One technique that contributed to TMS–EEG development is the application of blind source separation tools, such as independent component analysis (ICA), for the removal of TMS-related artifacts (Ilmoniemi and Kičić, 2010; Rogasch et al., 2014). These processing tools are based on the assumptions that EEG signals originate from temporally and spatially independent sources and that EEG signals can be modeled as a linear combination of cortical and non-cortical sources with independent time courses (Onton et al., 2006). However, one should keep in mind that ICA may not separate the artifacts correctly if the assumption of independence is not valid. Similarly, principal components analysis (PCA), initially applied to remove eye blink artifacts in EEG signals (Berg and Scherg, 1994), can be used to separate TMS-related artifacts from brain signals. These methods are based on a linear combination of orthogonal principal components and have been used to remove TMS-related artifacts in EEG signals (e.g., (Litvak et al., 2007; Korhonen et al., 2011; Rogasch et al., 2014)). Techniques that do not rely on the uncertain assumption of independence have been developed and applied to TMS–EEG such as signal-space projection (Ilmoniemi and Kičić, 2010; Mäki and Ilmoniemi, 2011; Mutanen et al., 2016), weighted forward-backward prediction with local state space models (Kimiskidis et al., 2013) and modelling of sources and artifacts (Ilmoniemi and Kičić, 2010; Mäkelä et al., 2018). The artifact correction with ICA and PCA uses the information from all the electrodes to smooth the signals, but when the intensity of the TMS related artifacts is locally concentrated, e.g., due to the type of coil, the correction may not be effective. In such cases, per electrode artifact correction may be a better strategy.

In recent years, the range of analysis tools for artifact removal has been rapidly growing. Most studies use common EEG analysis software toolboxes such as Fieldtrip (Oostenveld et al., 2011) and EEGLAB (Delorme and Makeig, 2004), but also combine their use with custom-written scripts on the Matlab platform. This complexity and the lack of a common "gold standard" analysis approach currently limit the implementation of TMS–EEG laboratories that do not have a strong expertise in scripting/coding (Atluri et al., 2016; Rogasch et al., 2017), such as in clinical settings where this expertise may not be available. Moreover, this also contributes to the current heterogeneity in techniques employed and restricts generalization of results between studies. As such, the very recent publication of two open-source analysis approaches for TMS–EEG pre-processing, i.e., TESA software (Rogasch et al., 2017) and TMSEEG toolbox (Atluri et al., 2016), as well as functionality within the FieldTrip toolbox (Herring et al., 2015), is an important step towards a standardization of TMS–EEG analysis procedures and will definitively facilitate the development of the field in the upcoming years.

4. Outcome measures of TMS–EEG and neurophysiological derivations

When the artifacts resulting from TMS are accounted for, TMS–EEG permits the direct recording of TMS-induced cortical activations with high temporal resolution (Ferreri and Rossini, 2013), without requiring participant cooperation, making it highly useful to study specific clinical populations (Rosanova et al., 2012) or physiological states. Several neurophysiological mechanisms can be assessed via this multimodal approach such as cortical reactivity, excitation and inhibition in local and distal regions, effective connectivity within the same or between the two cortical hemispheres, and neural plasticity.

4.1. TEPs and cortical evoked activity

The TMS-evoked potential is a complex waveform time-locked to the TMS pulse; composed of a series of peaks and troughs at specific latencies, it can last 300 ms or more (Hill et al., 2016). TEPs have been characterized following stimulation of several different cortical regions in healthy volunteers (Rosanova et al., 2009), the most studied region being the primary motor cortex (M1).

4.1.1. Current knowledge on TEPs

TEPs have many advantages over MEPs in the study of cortical excitability. Firstly, they are measurable at subthreshold intensities in M1, i.e., at least as low as 40% of the MEP threshold, exemplifying the sensitivity of the measure (Komssi et al., 2004; Komssi and Kähkönen, 2006). Secondly, from early investigations, it is known that TEPs can be recorded both locally, and in distal electrodes, allowing for the study of the spreading of activation over cortical areas (Ilmoniemi et al., 1997; Komssi et al., 2002). Consistent with MEPs (Di Lazzaro et al., 2018), TEPs are sensitive not only to the intensity of stimulation (Komssi et al., 2004; Kähkönen et al., 2005b; Casarotto et al., 2010), but also to the orientation of the coil and, hence the direction of induced current in the brain (Bonato et al., 2006; Casarotto et al., 2010). TEPs are also sensitive to brain state, e.g., to movement initiation (Nikulin et al., 2003), to vigilance state (e.g., sleep (Massimini et al., 2005)), and to the cortical site of stimulation (Komssi et al., 2002; Kähkönen et al., 2004, 2005a; Fitzgerald et al., 2008; Rosanova et al., 2009; Casarotto et al., 2010). Moreover, TEPs are only evoked following stimulation of intact and functional regions of the cortex (Gosseries et al., 2015), providing direct evidence that TEPs reflect cortical activity as opposed to electrical or physiological artifacts. TEPs are also highly reproducible within individuals over occipital, parietal, premotor, motor and prefrontal regions (Lioumis et al., 2009; Casarotto et al., 2010; Kerwin et al., 2018).

Over M1, TEPs are characterized by the following peaks: N15, P30, N45, P55, N100, P180 and N280 (Komssi and Kähkönen, 2006; Lioumis et al., 2009). When TMS is applied over the left M1, the initial N15 peak occurs in electrodes over the stimulated area, and the peak distribution then spreads over central sites (P30) and contralateral regions (N45). A bilateral distribution over central and centrofrontal sites characterizes later TEPs peaking at 100 ms and 180 ms, respectively (Nikulin et al., 2003; Bonato et al., 2006; Kicić et al., 2008). The latency of these peaks can vary and some peaks are more reliable than others—such as P30, N45 and N100 (Lioumis et al., 2009). Further short-latency peaks have been reported (i.e., N7, P13); they may reflect additional, direct local cortical responses to the TMS pulse (Ferreri and Rossini, 2013), or contamination from TMS-evoked muscle activity (Mutanen et al., 2013; Rogasch et al., 2013b). As discussed in Section 5 paired-pulse and pharmacological studies have suggested that early peaks (N15–P30) are likely to reflect cortical excitatory activity, while later peaks (N45–N100) are linked to cortical inhibition.

Apart from M1, TEPs are well characterized to date in the dorsolateral prefrontal cortex (DLPFC). TEPs recorded from the DLPFC show peaks at P25, N40, P60, N100 and P185 with generally smaller responses when compared with M1 (Kähkönen et al., 2005b; Lioumis et al., 2009). The initial N40 peak typically occurs in elec-

trodes over the stimulated area, and the peak distribution then spreads over central and contralateral frontal sites (P60). As for M1, the N100 and P180 are characterized by a large spread of activity over bilateral central sites. DLPFC TEPs have recently been shown to display high concordance and low measurement errors, and good within- and between-session reliability, with N100 and P180 showing the greatest test-retest reliability (Kerwin et al., 2018).

TEPs in other non-motor regions are less well characterized than DLPFC. However, it is now well established that TEPs from non-motor regions typically display lower amplitudes than M1. To this date, many regions have been stimulated, such as the premotor cortex (Zanon et al., 2013; Fecchio et al., 2017; Salo et al., 2018), supplementary motor area (Salo et al., 2018), posterior parietal cortex (Romero Lauro et al., 2014), and occipital cortex. Lack of consistency in methods employed to characterize TEPs do not allow for a "standardized" characterization of the peaks and spatio-temporal distribution of activity in those regions. This particular issue is discussion in Section 7 of the review.

The knowledge discrepancy between motor and non-motor areas could be related to the extensive literature on TMS-EMG and on the cytoarchitecture of M1 which have definitively contributed to the focus of TMS-EEG studies on M1. In addition, the detailed characterization of TEPs from M1 could also be related to the peculiar cytoarchitecture of M1, as the magnetic pulse may be more effective in activating longitudinally oriented pyramidal neurons than in other non-motor regions, and therefore producing more reliable TEPs with higher amplitudes.

In fact, many aspects of TEPs remain to be better characterized such as their morphology and physiology in different non-motor regions (Hill et al., 2016), test-retest reliability of peaks measured in several non-motor regions, the specific origin of each of the TEPs peaks, the exact involvement of somatosensory and auditory evoked responses in specific cortical regions (Miniussi and Thut, 2010) and the involvement of subcortical structures in their generation.

4.1.2. How do we measure TEPs?

One of the most common approaches for quantifying TEPs is to measure the amplitude and latency of the TEP peaks over subsets of electrodes, i.e., electrodes of interest (EOI) (Hill et al., 2016). Determination of which electrodes to use in EOI analyses is determined *a priori* based on scalp locations where responses are expected (e.g., site of stimulation) or is derived using data-driven methods, such as cluster-based permutation statistics. Data are typically presented as a waveform of varying amplitude as a function of time (Fig. 1). Moreover, scalp voltage distributions are typically presented as maps for each peak of interest, allowing for visualization and quantification of the spread of activity at selected time points across the cortex in relation to the origin ROI.

An alternative to measuring TEP peak amplitudes and latencies is to measure the area under the curve (i.e., the integral) of the rectified signal or standard deviation (root mean square) across specific EOI at a given point in time corresponding to TEP peaks. This measure has been called either local mean field power (LMFP) (Pellicciari et al., 2013; Romero Lauro et al., 2014) or cortical evoked activity (CEA) (Rajji et al., 2013). The advantage of LMFP/CEA is that it takes into account the width as well as the peak of the evoked activity, and does not require an obvious main peak to be present. However, this approach ignores the polarity of the signal, which could yield important information on the nature of the underlying source. Derived measures of LMFP include immedi-

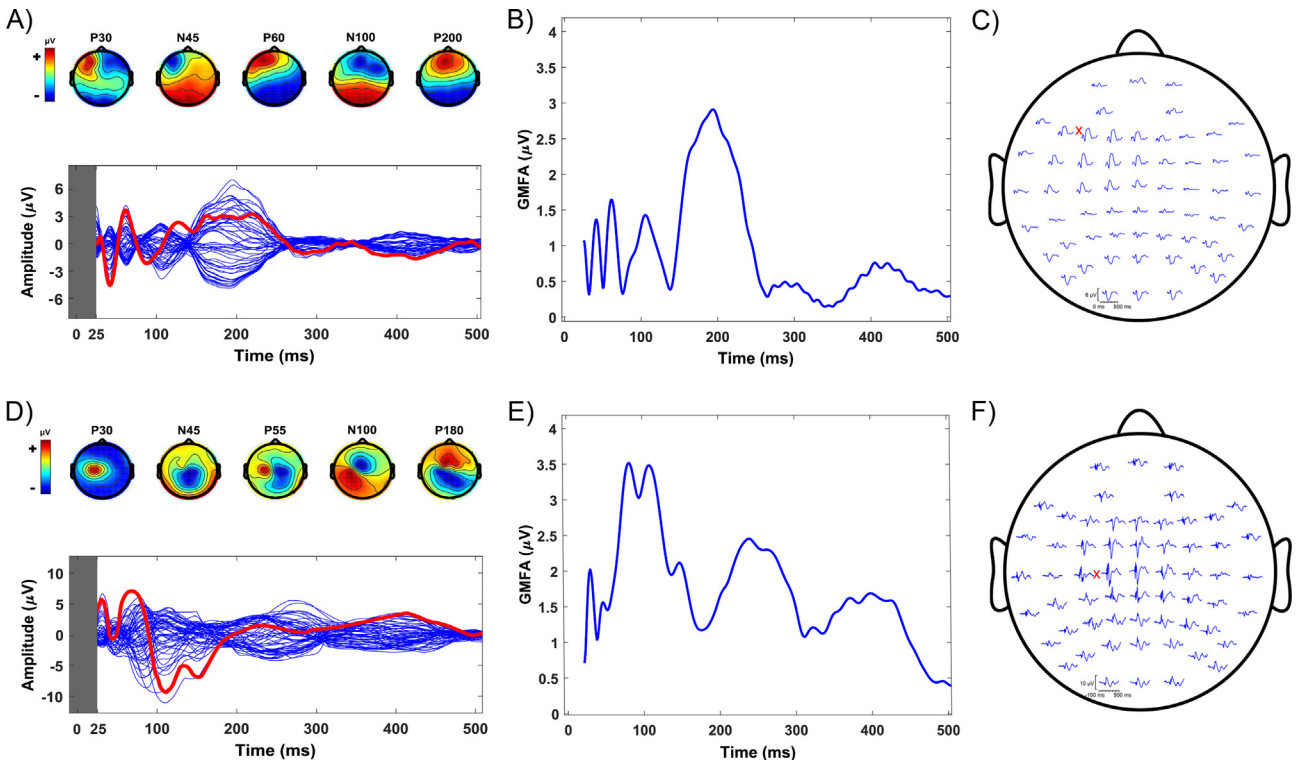

Fig. 1. Sample data of TMS-evoked activity recorded with EEG following single pulse stimulation in a representative subject (60 channels). The top row of the figure depicts left dorsolateral prefrontal cortex stimulation, while the bottom row of the figure depicts left primary motor cortex stimulation. (A) and (D) butterfly plots and topographical maps of the main TEPs for the 60 recorded channels. The red line corresponds to the respective electrode of interest (i.e., F5 and C3). The grey box indicates removed data points due to TMS-related artefacts. (B) and (E) Data shows the global mean field amplitude (GMFA) of TMS-evoked potentials. (C) and (F) Scalp maps presenting butterfly plots for each individual electrode. The red "x" corresponds to area of stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ate response area (IRA), which assesses the local and immediate response to TMS (Casarotto et al., 2013). The slope of the first EEG component, i.e., immediate response slope (IRS), has also recently been assessed, based on animal studies that suggest it could be a marker of synaptic strength (Casarotto et al., 2013; Huber et al., 2013; Canali et al., 2014).

An alternative to measuring activity within specific EOIs is to measure the impact of the TMS pulse on activity evoked across all electrodes (the global mean field power/amplitude; GMFP/GMFA) (Fig. 1C), which is the averaged signal of TMS activity over the entire surface of the head, or the standard deviation (root mean square) across electrodes at a given point in time (Lehmann and Skrandies, 1980; Komssi et al., 2004; Esser et al., 2006).

Finally, it is also possible to measure TEPs following paired-pulse protocols (see Section 5.1 for a more detailed description), in which two pulses are delivered at certain short inter-stimulus intervals. These are usually analyzed in the same way as single pulse TEPs, however, the influence of the first (conditioning) pulse on the signal of the second (test) pulse needs to be removed by subtracting the time-shifted single pulse data (see Rogasch et al., 2015). Differences in TEP component amplitudes between the conditioned and unconditioned test pulses can then be compared. Alternatively, mean CEA over a specific time frame (e.g., 50–150 ms) (Daskalakis et al., 2008), and in data filtered into specific frequency bands (Farzan et al., 2009) has also been used to compare between paired- and single-pulse conditions. Recent studies have also shown that by combining TMS–EEG with peripheral nerve stimulation, it is possible to study afferent inhibition in different cortical areas (Bikmullina et al., 2009; Ferreri et al., 2012; Noda et al., 2016).

Each of the above-described methods allows to draw a different portrait of TEPs and the choice of the preferred method is highly dependent on the goal of the study and the hypothesis. The use of EOI is particularly relevant when there is a clear *a priori* hypothesis on the location of the expected brain response evoked by TMS. This method is not optimal when there is a big TMS artifact as it can mask the TEP peaks. The LMFP method is relevant when there is an *a priori* hypothesis related to an expected change in brain activity that is localized and not related to a specific TEP peak. Finally, the GMFP analysis is the method of choice when there is no *a priori* hypothesis with regards to local activity, but rather when the goal is to explore global brain activity following the TMS pulse. It should be noted that both GMFP and LMFP allow for comparison of multiple stimulation sites, such as M1 and DLPFC (Kähkönen et al., 2005a; Fecchio et al., 2017). An alternative approach to collapsing data using EOI, LMFP or GMFP is to compare all TEP data points across space and time using non-parametric, cluster-based permutation tests (e.g. (Dominguez et al., 2014; Premoli et al., 2014a, 2014b, Rogasch et al., 2014, 2015)). This class of statistical methods can take in to account any combination of space, and time (and also frequency), while controlling for the multiple comparisons problem inherent in mass-univariate analyses (Maris and Oostenveld, 2007). Cluster-based permutation methods are advantageous as they are robust for both exploratory (i.e. no specific *a priori* hypothesis as to when or where differences are expected between conditions or groups) and hypothesis-driven comparisons of TEP amplitudes (and oscillations). Furthermore, cluster-based permutation methods do not require assumptions of data normality, as a null distribution is derived from the data itself.

4.2. TMS-related cortical oscillations

Cortical oscillations have been widely studied in the EEG literature and specific frequency bands have been associated with specific behaviors or cognitive functions as well as with specific cortical and sub-cortical regions (Thut and Pascual-Leone, 2010). Canonical frequency bands include the following: (1) delta (deltaδ): 0–4 Hz, prominent in deep-sleep and involved in motivational drive; (2) theta (thetaθ): 4–8 Hz, typical during deep sleep, involved in memory and prefrontal cognitive processes; (3) alpha (alphaα): 8–13 Hz, prominent when eyes are closed or during state of drowsiness/relaxation, involved in cognitive inhibition, prominent in occipital cortex; (4) beta (betaβ): 13–30 Hz, prominent when alert and active, involved in motor control, prominent in frontal/central regions; and (5) gamma (gammaγ): 30–70 Hz, reflecting short-range cortical feedback loops and activity of fast-spiking inhibitory interneurons, involved in higher cognitive processes, prominent in frontal regions.

Investigations of cortical oscillations focus on the study of TMS-induced effects in the frequency domain, as TMS is thought to interact with local and distant cortical oscillations. The added value of TMS–EEG in the study of TMS-induced effects on cortical oscillations is the possibility to study the functional specificity of brain rhythms (Thut and Miniussi, 2009), as well as to probe thalamocortical circuits via direct measurement of TMS-evoked oscillatory activity that results from phase-reset by TMS (Rosanova et al., 2009; Herring et al., 2015; Canali et al., 2017). As such, TMS–EEG provides the opportunity to measure activity in frequency bands directly evoked by the TMS pulse, which is depicted as a transient phase alignment of the oscillatory activity (Thut et al., 2011; Kawasaki et al., 2014). By this means, it allows for the study of the natural or resonant frequency in a specific region, reflected in a brief period of synchronization of neuronal firing at a specific frequency following the TMS pulse (Van Der Werf and Paus, 2006; Rosanova et al., 2009; Herring et al., 2015). On the other hand, ongoing brain oscillations, likely reflecting momentary brain state, have been shown to determine TMS-evoked MEP amplitudes. For instance, MEP amplitude is correlated with pre-TMS activity in the beta (Mäki and Ilmoniemi, 2010; Schutter and Hortensius, 2011) and gamma (Schutter and Hortensius, 2011) frequency ranges (see also (Thut et al., 2017) for a recent review on the usefulness of oscillatory EEG measures in guiding TMS interventions). As outlined in Sections 5 and 6 below, cortical oscillations have provided important insights in the effects of plasticity-inducing protocols on brain activity in healthy subjects, in the effect of specific treatments in clinical populations and the role of a specific oscillatory network in the pathophysiology of clinical disorders (Assenza et al., 2017).

Oscillatory characteristics evoked by TMS in various regions of the brain have been well defined in recent years. For instance, in non-motor regions, among the several parameters that allow to characterize the TEPs, spectral features of the TMS-evoked response seem to provide interesting and consistent results. Specifically, TMS evokes α- and γ-band oscillations in occipital regions (Rosanova et al., 2009; Pigorini et al., 2011; Herring et al., 2015), β-band oscillations in parietal regions (Rosanova et al., 2009), β- and γ-band oscillations in the premotor cortex (Canali et al., 2017), and α-band (Pigorini et al., 2011) and fast β- and γ-band oscillations in frontal regions (Rosanova et al., 2009).

4.2.1. How do we measure TMS-related cortical oscillations?

In a recent review, Pellicciari and colleagues thoroughly described the methodology and important factors to consider when analyzing cortical oscillations in the time-frequency domain (Pellicciari et al., 2017b), while Farzan et al. (2016) presented a summary of the different types of analysis. Briefly, the most frequently employed method is to analyze data using a time–frequency approach, such as wavelet decompositions and short-time Fourier transforms, where a sliding window is used to measure TMS-evoked oscillatory power across time and frequency (Farzan et al., 2016; Pellicciari et al., 2017b). Notably, the time–

frequency characteristics of TEPs obtained from M1, when stimulated at resting motor threshold or supra-threshold intensity, are significantly affected by the presence of peripheral MEPs (Fecchio et al., 2017). TMS-evoked oscillations can be assessed in two ways: (1) the evoked oscillatory response (EOR), which involves applying the time–frequency decomposition to the data averaged across trials (e.g., the TEP) and returns information only on oscillations phase-locked to the TMS pulse (i.e., evoked oscillations); and (2) total oscillatory response (TOR; also called event-related spectral perturbation, ERSP), which involves applying the time–frequency decomposition to individual trials, and therefore captures both the phase-locked and non-phase locked oscillations following TMS (i.e., evoked and induced oscillations) (Herrmann et al., 2014). One interpretation of TMS-induced oscillations is to consider the so-called 'natural frequency', which is calculated as the frequency with the largest cumulated ERSP over time per stimulation node, and which is thought to reflect the intrinsic dynamics of the corresponding cortico–thalamic circuits (Rosanova et al., 2009). An alternative time–frequency analysis is inter-trial coherence (ITC) or phase-locking factor, which measure phase coherence across trials at single channels, as well as the event-related cross-coherence which computes phase coherence between two channels (Delorme and Makeig, 2004). See Fig. 2 for a typical example of TMS-evoked cortical oscillations. As for TEPs, cortical oscillations can also be assessed following TMS protocols other than single pulse, such as paired-pulse paradigms (see Section 5.1).

4.3. Source localization and cortical connectivity

Although development of imaging techniques such as fMRI and positron emission tomography have greatly contributed to the understanding of brain networks, they are limited by the correlational nature of the cortical relationships they assay. When compared with TMS, these neuroimaging techniques are limited by their poor temporal resolution making it difficult to study in detail the sequence of activation (Rogasch and Fitzgerald, 2013) or to understand true neuronal physiological function. Notably, TMS–EEG offers unique insights into the study of effective connectivity, defined as the causal relationships of neuronal activity between regions (Friston et al., 1993). The use of TMS–EEG to infer effective connectivity has been recently reviewed by Bortoletto and colleagues (Bortoletto et al., 2015). Specifically, when a TMS pulse is applied to a specific brain region, EEG can be used to assess the propagation of the signal in time and space to anatomically and functionally connected brain regions (Bortoletto et al., 2015; Kitajo et al., 2015; Bergmann et al., 2016). This permits investigation of brain networks involved in different cognitive processes and brain states, as well as the reorganization of networks in clinical populations.

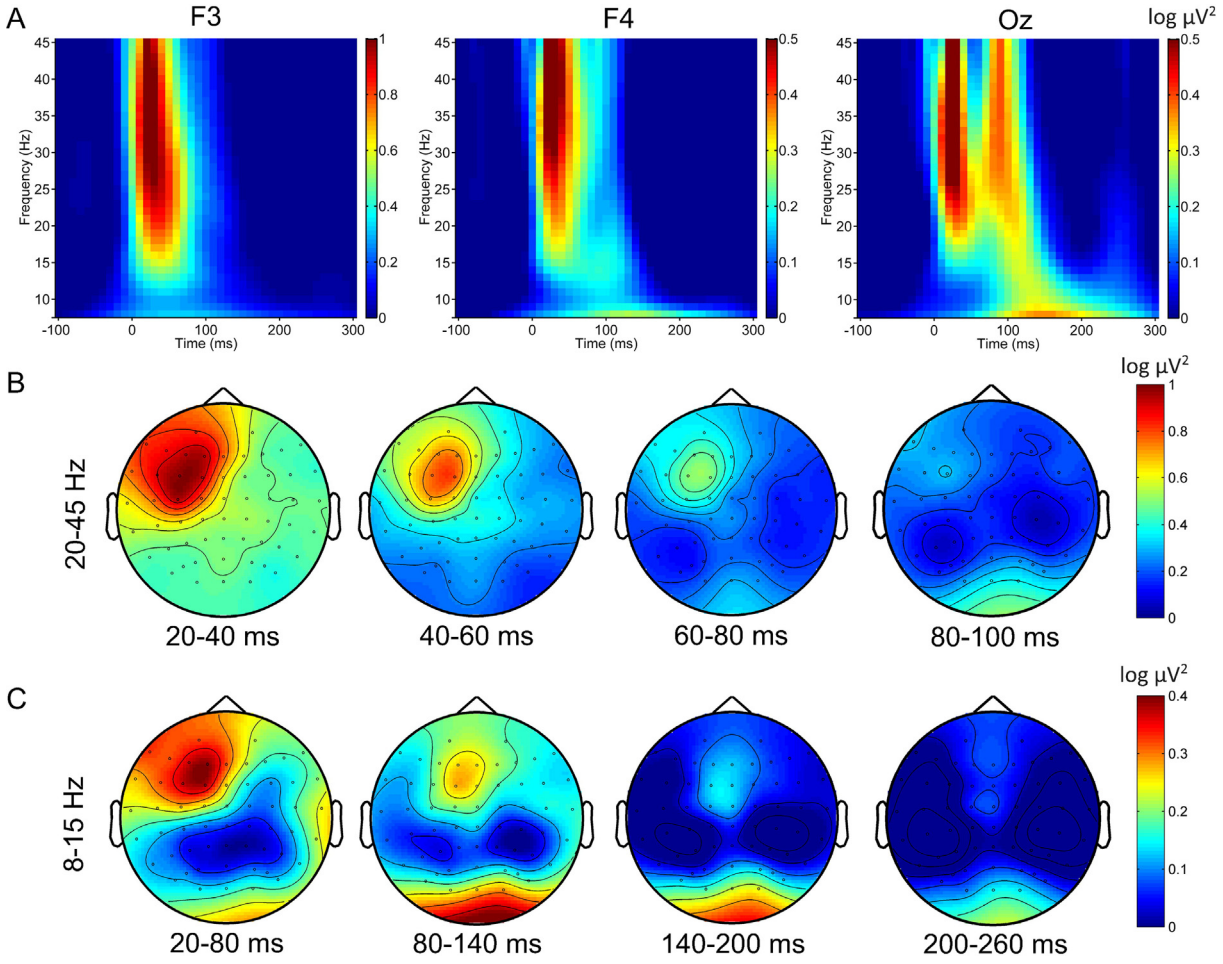

Fig. 2. Group data displaying TMS-evoked oscillatory activity over left dorsolateral prefrontal cortex. (A) Time-frequency plots of TMS-evoked oscillations at three different electrodes. Topographies of TMS-evoked oscillations are displayed (B) over the first 100 ms between 20 and 45 Hz and (C) over the first 260 ms between 8 and 15 Hz (from *NeuroImage*, 101, Rogasch et al. Removing artefacts from TMS-EEG recordings using independent component analysis: Importance for assessing prefrontal and motor cortex network properties, 425–439, Copyright (2014), with permission from Elsevier).

4.3.1. How do we perform source localization and measure connectivity?

Source localization is based on the knowledge and computation of conductivity structure of the head to locate and quantify current origin and distribution (Ilmoniemi and Kičić, 2010). The estimation of the neural sources that generate the EEG signals is a difficult and ill-posed problem. There are available methods for the inverse transform from the sensor to the source space, such as the standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui et al., 2002), which permits the localization of activity occurring at each peak of evoked activity, such as GMFP, and can be then mapped at the cortical surface. When combined with precise source localization, detailed effective connectivity measurements can be produced from TMS–EEG. For instance, progress in source localization modeling techniques and the use of high-density EEG (64–256 electrodes) now allows for a sensitive assessment of source generators of the EEG signal (Lucka et al., 2012).

Moreover, Casali et al. (2010) recently developed novel analystic tools to characterize the TMS–EEG evoked response. Combined with precise source modeling, these measures quantify the spatiotemporal distribution of absolute amplitude of cortical currents evoked by TMS (significant current density, SCD), the temporal modulation of TMS-evoked connectivity (significant current scattering, SCS) and phase resetting of ongoing cortical oscillations (phase-locking, PL). The same group also recently developed the perturbational complexity index (PCI), an index of the integration of activity by the thalamocortical system which measures the complexity of the brain response to TMS and aims at assessing levels of consciousness (Casali et al., 2013) (see Fig. 3). A low PCI results from reduced integration across cortical areas or a lack of differentiation of cortical responses (stereotypical activity), while high PCI reflects integrated and differentiated spatiotemporal activations.

Several methods exist to assess connectivity of TMS–EEG signals. It is possible to explore the signal propagations via the spatio-temporal distribution of TEPs as well as evoked oscillatory activity (Miniussi and Thut, 2010). In a different approach, the TMS-induced coherence and synchrony in the amplitude or phase of EEG evoked activity in different brain regions is assessed (Bortoletto et al., 2015). For this, many measures of functional and effective connectivity are developed (Schoffelen and Gross, 2009; Sakkalis, 2011; Greenblatt et al., 2012; Kida et al., 2016), which can further be used to form complex networks mapping the brain connectivity (Fornito et al., 2016; Kida et al., 2016).

In TMS–EEG studies, the connectivity analysis aims to quantify the relationship between cortical regions following stimulation. In a recent study (Petrichella et al., 2017), using the connectivity measure of directed transfer function (DTF) and source localization, it was found that trials resulting in MEPs had higher outflow connectivity from M1 to other cortical regions and higher inflow connectivity between somatosensory cortex and M1 than trials without MEPs at ~60, 100 and 160 ms. These results suggest that the latter TEP components, particularly the P60, could be contaminated by re-afferent input from the periphery as a result of finger movement evoked by TMS. A second study compared TMS-evoked effective connectivity following stimulation of premotor and superior parietal cortex to structural connectivity measured using diffusion weighted imaging (Amico et al., 2017). Effective connectivity was stronger in the beta range for parietal cortex, and beta/gamma range for premotor cortex. However, structure/function correlations across the entire brain decreased following stimulation across all frequency bands at both sites, suggesting a complex relationship between TMS-evoked and anatomical connectivity. In connectivity analysis of TMS–EEG from patients with epilepsy, using the multivariate measures of partial directed coherence, PDC (Kimiskidis et al., 2013) and partial mutual information from mixed embedding, PMIME (Kugiumtzis and Kimiskidis, 2015; Kugiumtzis et al., 2017), a change of connectivity before and after TMS was reported. In focal as well as in genetic generalized epilepsy, it was found that the connectivity network decreases in density during the epileptiform discharge. The abortion of the epileptiform discharge by TMS results in the restoration of network structure in a similar way as for spontaneous epileptiform discharge termination. In sum, the temporal resolution of EEG is ideally suited for measuring the fast spread of activity following TMS and there are now several approaches for quantifying effective connectivity by using TMS–EEG.

5. TMS–EEG in the study of healthy human neurophysiology

5.1. TMS protocols for assessment of cortical inhibition and excitation

Various single-pulse and paired-pulse TMS–EMG techniques enable the assessment of M1 inhibition and excitation (Hallett, 2007; Rossini et al., 2015). These protocols have also been employed in TMS–EEG paradigms and exploited outside of M1, opening a large range of possibilities for the study of excitatory and inhibitory activity in the cortex. The rationale behind their use in TMS–EEG studies is that the intracortical inhibitory or excitatory processes indexed by a change in the amplitude of EMG-related MEPs could also be quantifiable via TEPs and TMS-evoked measures such as evoked cortical oscillations. Thus far, studies have assessed five different protocols that will be described in the following subsections, namely long-interval intracortical inhibition (LICI, Section 5.1.1), cortical silent period (CSP, Section 5.1.2) short-interval intracortical inhibition (SICI, Section 5.1.3), intracortical facilitation (ICF, Section 5.1.3), and short-latency afferent inhibition (SAI, Section 5.1.4), on TMS–EEG responses in healthy volunteers. The main results are presented in Table 1 and summarized below. Because these protocols are used in clinical studies, it is important to first review their neural effect in healthy volunteers.

5.1.1. Long-interval intracortical inhibition (LICI)

LICI is obtained when two suprathreshold stimuli are applied at intervals between 50 and 200 ms, and is thought to reflect GABA-B receptor (GABABR) mediated neurotransmission (McDonnell et al., 2006; Florian et al., 2008). Daskalakis and colleagues first demonstrated that it is possible to record a reduction in mean cortical evoked EEG activity following the application of LICI applied over M1 and the DLPFC (Daskalakis et al., 2008). They showed significant suppression of the averaged EEG signal at 50–150 ms following the TS, which was strongly correlated with the MEP suppression recorded in hand muscles. In a follow-up study, LICI was also shown to be related to reduced cortical evoked activity when applied to the parietal cortex, suggesting that it can be recorded in various non-motor cortical areas (Fitzgerald et al., 2008). The time course of LICI-related inhibition of cortical evoked activity was further studied in the DLPFC and parietal cortex (Fitzgerald et al., 2009a). Maximal inhibition was observed from 100 to 150 ms, similar to the time course associated with the late peak of GABAB-ergic activity. Similar reductions were obtained when looking specifically at TEPs. One study showed suppression of the P30, N45, N100 and P180 following LICI over M1 (Premoli et al., 2014b). In contrast, the P70 peak was increased in amplitude, suggesting that LICI may not always result in TEP suppression. Rogasch and colleagues (Rogasch et al., 2015) showed that DLPFC LICI produces significant suppression of N40, P60 and N100 components.

The impact of LICI on oscillations was also explored. Farzan et al. (2009) explored the impact of LICI on gamma oscillations and showed that it is associated with a significant inhibition of TMS-evoked gamma oscillations in the DLPFC, but not M1

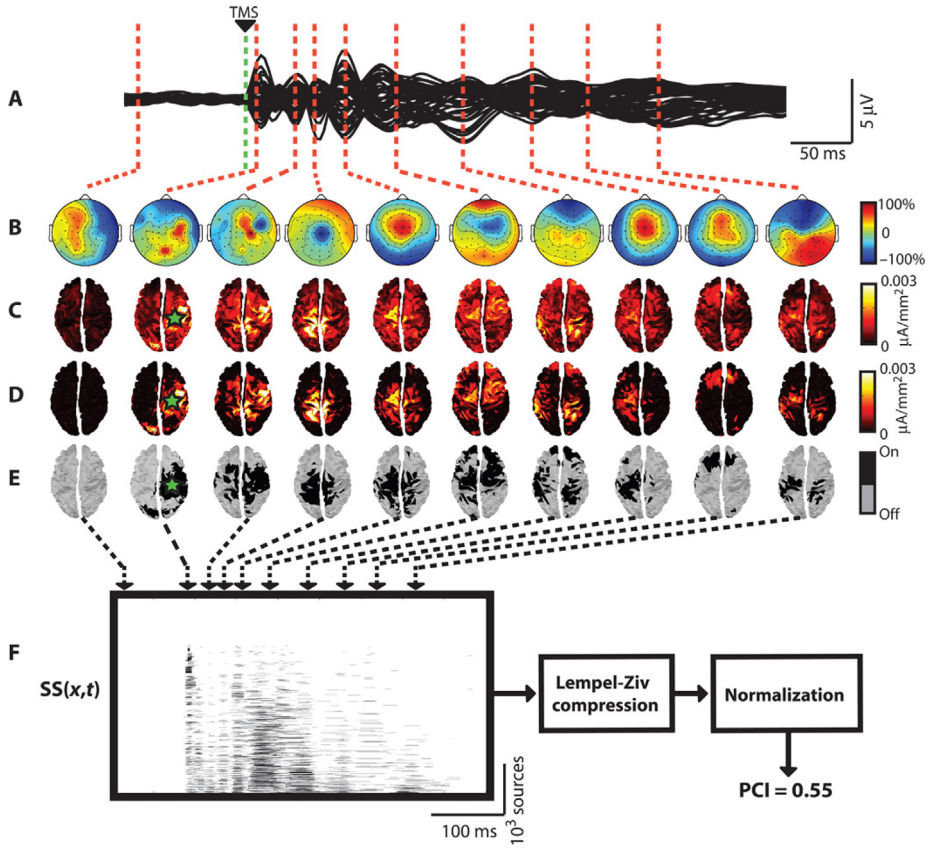

Fig. 3. Cortical connectivity as measured by the perturbational complexity index (PCI). (A) Butterfly plot of TMS-evoked potentials recorded from 60 EEG channels. (B) Voltage distribution maps in correspondence to selected peaks. (C) Corresponding distribution of cortical currents. (D) Significant TMS-evoked cortical currents estimated by nonparametric statistics. (E) Binarization of statistically significant cortical currents. (F) Statistically significant sources are sorted in matrix SS(x,t), from bottom to top, on the basis of their total activity during the post-stimulus period. The information content of SS is estimated by calculating the Lempel-Ziv complexity measure. PCI is defined as the information content of SS, normalized by the correspondent source entropy. (from *Science Translational Medicine*, 5(198), Casali et al. A theoretically based index of consciousness independent of sensory processing and behavior, 198ra105-198ra105, Copyright (2013), with permission from the American Association for the Advancement of Science (AAAS)).

(Farzan et al. 2009, 2010b). Rogasch and colleagues (Rogasch et al. 2015) showed a suppression of TMS-evoked gamma and beta oscillations, and a spread of inhibition across fronto-central and contralateral fronto-temporal regions from 109 to 280 ms.

Other TMS–EEG studies of LICI mechanisms explored more specific aspects of the cortical evoked response to LICI. The reliability of TMS–EEG measures of LICI was explored; the results showed high test–retest reliability for both M1 and DLPFC applications (Farzan et al., 2010b). In addition, by varying the intensity of both the CS and TS was shown that early (*i.e.,* P30 and P60) and late TEPs (*i.e.,* N100) associated with LICI may represent different mechanisms (Rogasch et al., 2013a). Another study suggested that LICI produces a strong inhibition in the time–frequency domain using novel methods of analysis that consider clusters across time, frequency and space (Dominguez et al., 2014). Finally, Opie and colleagues directly compared inter-stimulus intervals (ISIs) of 100 and 150 ms over M1; they found that these ISIs may relate to slightly differential contributions of the GABAergic circuit to LICI, with a specific inhibition of P30 at an ISI of 100 ms and topographical differences in global suppression of cortical evoked activity for the P30, N40 and P180 components (Opie et al., 2016).

5.1.2. Cortical silent period (CSP)

The CSP is also a marker of inhibition of cortical activity, presumably of GABABR-mediated neurotransmission (Ziemann et al., 2015), and is obtained when a TMS pulse is delivered during tonic contraction of the target muscle (Merton and Morton, 1980). Although this measure cannot be exploited outside of M1 due to its dependence on muscle activation, one study explored the use of TMS–EEG to assess the cortical evoked response to CSP (Farzan et al., 2013). It was found that CSP correlated with several aspects of the EEG signal, including the amplitude of global cortical evoked activity in the ipsilateral motor cortex, the duration of the TEP in the ipsilateral motor cortex, the amplitude of the N100 and N280, as well as power in the delta to alpha frequency band in local and distal areas. This suggests that TEPs can capture electrophysiological correlates of the CSP and TMS–EEG may serve as a complementary measure to TMS–EMG to study long-lasting GABABergic inhibition.

5.1.3. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

In SICI, a subthreshold CS inhibits a suprathreshold TS-elicited MEP at ISIs of 2–3 ms while longer ISIs (7–30 ms) produce facilitation of MEPs, *i.e.,* IFC (Kujirai et al., 1993). In the TMS–EMG literature, SICI protocol is associated to GABAA receptor (GABAAR) activity (Ziemann et al., 1996), while the excitation produced by the ICF has been associated to both GABAAR (Ziemann et al., 1996) and NMDAR (Ziemann et al., 1998).

SICI was assessed with TMS–EEG in one of the early studies, in a small sample of 5 individuals (Paus et al., 2001). No difference was found in TEP amplitude between single pulse and SICI, while ICF was associated with reduced amplitude of P30 and N45. More recently, Ferreri et al. (2011) explored the effect of SICI and ICF over M1 and showed bidirectional modulations of the P30 and

Table 1
TMS–EEG measures of cortical inhibition and excitation.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
LICI						
Daskalakis et al. (2008)	15 HS 9 HS	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC) Sham LICI (subset of samples)	CEA (50–150 ms)	(1) LICI: ↓ mean CEA over M1 and DLPFC (2) Significant correlation between EEG and EMG measures of LICI over M1 (3) Significant correlation between LICI suppression in DLPFC and M1
Fitzgerald et al. (2008)	14 HS 5 HS	Left M1 Left DLPFC Left parietal	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC)	CEA (30–300 ms)	(1) LICI: ↓ mean CEA over all three regions (2) No correlations between EEG measures of LICI in the three regions
Fitzgerald et al. (2009)	14 HS 5 HS	Left M1 Left DLPFC Left parietal	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC)	CEA (every 25 ms)	(1) LICI: ↓ mean CEA from 75–125 ms and 220–225 ms (M1), 50–100 ms (DLPFC), 50–175 ms (parietal)
Farzan et al. (2009)	14 HS	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC) Sham LICI (subset of samples)	CEA Cortical oscillations	(1) M1-LICI: ↓ mean CEA and of delta, theta and alpha bands (2) DLPFC-LICI: ↓ mean CEA and of all frequency bands, with maximal suppression of gamma (3) Trend for higher suppression of alpha in DLPFC vs M1
Farzan et al. (2010b)	36 HS 30 HS (14 HS test-retest)	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC) Sham LICI (subset of samples)	CEA Cortical oscillations	(1) LICI: ↓ mean CEA over M1 and DLPFC (2) Significant correlation between EEG measure of LICI and EMG measures of LICI and CSP over M1 (3) High reproducibility and consistency of EMG and EEG measures of LICI in M1 and DLPFC (4) M1: ↓ delta, theta and alpha bands; DLPFC: ↓ all frequency bands 5) Stronger suppression of high-frequency bands (beta, gamma) in DLPFC
Rogasch et al. (2013)	8 HS	Left M1	13 channels Sampling rate: 10 KHz	Paired pulse (biphasic, 1 mV, 110–125-140% of RMT) ISI: 100msNo neuronav	TEPs (P30, P60, N100)	(1) Increasing conditioning and test pulse intensity results in increased inhibition of early TEPs (P30, P60) following LICI while N100 is unchanged (2) Significant correlation between LICI-P30 and LICI-EMG
Dominguez et al. (2014)	33 HS	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation (DLPFC)	CEA (time-frequency-spatial domains)	(1) LICI produces a robust and strong inhibition in the time frequency domain (using both methods of analysis) (2) Spatial pattern of inhibition differs between single and paired pulse
Premoli et al. (2014)	19 HS	Left M1	64 channels Sampling rate: 5000 Hz	Paired pulse (monophasic, 100%RMT) ISI: 100 ms	TEPs	LICI at baseline (i.e. pre-drug intake) characterized by ↓ P25, N45, N100 and P180; and ↑ P70
Rogasch et al. (2015)	30 HS	Left DLPFC	57 channels Sampling rate: 20 KHz	Paired pulse (monophasic, 1 mV) ISI: 100 ms	TEPs Cortical oscillations	1) LICI: ↓ N40, P60 and N100 (2) Inhibition spreads from DLPFC towards fronto-central and contralateral frontal/temporal regions from 109 to 280 ms (3) LICI: ↓ beta and gamma power
Opie et al. (2016)	12 HS	Left M1	59 channels Sampling rate: 2048 Hz	Paired pulse (monophasic, 120% RMT) ISI: 100, 150 ms	TEPs	(1) LICI-100: ↓ P30, N100, P180 amplitude, significant correlation between slope of N100 and LICI MEPs (2) LICI-150: ↓ N100, P180 amplitude (3) Differential global topographical inhibition between 100 and 150 ms

Table 1 (*continued*)

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
CSP						
Farzan et al. (2013)	18 HS	Left M1	64 channels Sampling rate: 20 KHz	Single pulse (monophasic, 140% RMT)	TEPs (time-frequency and spectral power, GMFA)	(1) Significant correlation between duration of CSP and: – duration and amplitude of GMFA (r = 0.63; 0.66) – global TEP amplitude over bilateral motor, and contralateral fronto-temporal and parieto-occipital cortices (r = 0.71 to 0.83) – N100 and N280 amplitude (r = 0.71; 0.62) – duration of TEPs in ipsilateral motor cortex (r = 0.72) – delta to alpha power in bilateral motor, fronto-temporal and parietal regions (r = 0.74 to 0.84) – beta power in ipsilateral motor area (r = 0.76)
SICI and ICF						
Paus et al. (2001)	5 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single/paired pulse (monophasic, CS: 95% AMT, TS:0.5 mV) ISI: 3, 12 ms Neuronavigation	TEPs (GMFP)	(1) No difference between single pulse and SICI in TEPs (2) ICF: ↓ P30 and N45, ↓ oscillatory response
Ferreri et al. (2011)	8 HS	Left M1	19 channels Sampling rate: 2500 Hz	Single/paired pulse (biphasic, CS:80% RMT, TS:1mV) ISI: 3, 11 ms Neuronavigation	TEPs	(1) SICI: modulation of amplitude of early (↑ N7, P13, N18, N44; ↓ P30, N44, P60) and late (↑ N100, P180, N280; ↓ N280, P190) EEG evoked responses at different locations (2) ICF: modulation of amplitude of early (↑ P13, P30, N44, P60; ↓ N7, N44) and late (↑ N100, N280; ↓ N280) EEG evoked responses at different locations
Cash et al. (2017)	12 HS 21 HS (M1-ICF only)	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Single/paired pulse (monophasic, CS:80% RMT, TS:1mV) ISI: 2, 10 ms Neuronavigation	TEPs Cortical oscillations	(1) SICI-M1: ↓ TEP power in left central regions, ↓ amplitude of P30, N45, P60, ↓ power in theta, alpha, beta bands, correlation between SICI MEP and P30, P60 amplitude (2) SICI-DLPFC: ↓ TEP power in left frontal regions, ↓ amplitude of P60, ↓ power in alpha band (3) ICF-M1: ↑ TEP power in left central regions, ↑ amplitude of P60, ↑ power in alpha band (4) ICF-DLPFC: ↑ TEP power in left frontal regions, ↑ amplitude of P60, N100
Noda et al. (2017b)	12 HS (younger adults) 12 HS (older adults)	Left DLPFC	64 channels Sampling rate: 20 KHz	Single/paired pulse (monophasic, CS:80% RMT, TS:1mV) ISI: 2, 10 ms No neuronav.	TEPs Cortical oscillations	(1) Old-SICI: ↓ P60, P180; ↑ N100 (2) SICI old vs young: ↓ N100 in younger adults (3) Old-ICF: ↑ N45, P60; ↓ N100 (4) ICF old vs young: ↓ N45 and no effect on N100 in younger adults (5) positive correlation between: SICI P60 and N100; negative correlation between: SICI P60 and ICF P60; ICF N100 and SICI N100
SAI						
Bikmullina et al. (2009)	10 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse/SAI (monophasic, 1 mV) ISI: 25 ms Neuronavigation	TEPs (N100)	(1) SAI: ↓ N100 amplitude in left M1 (2) positive correlation between: ↓ MEPs and ↓ N100 amplitudes
Ferreri et al. (2012)	8 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse/SAI (monophasic, 120% RMT) ISI: N20 + 2 ms, N20 + 10 ms Neuronavigation	TEPs (GMFP, ITC) Cortical oscillations (ERSP)	(1) Global ↓ N100 amplitude (2) ↓ P60 amplitude in left M1 (3) Motor cortex beta rhythm selective decrease of inter-trial synchronization
Noda et al. (2016)	12 HS	Left M1 Left DLPFC	64 channels Sampling rate: 20 KHz	Single pulse/SAI (monophasic, 1 mV) ISI: M1-N20 + 2 ms, DLPFC-N20 + 2, 4, 6, 8, 10, 20 ms	TEPs	(1) M1: ↑ N45 and N100, ↓ P180 amplitude in left M1, correlation between N100 and MEP modulation (2) DLPFC: modulation of TEP power at N20 + 4 ms (3) DLPFC: ↓ P60, ↑ N100 amplitude in left frontal regions

Legend: AMT: active motor threshold; CEA: cortical evoked activity; CS: conditioning stimulus; DLPFC: dorsolateral prefrontal cortex; ERSP: event-related spectral perturbation; ICF: intracortical facilitation; ITC: intertrial coherence; ISI: interstimulus interval; GMFA: global mean field amplitude; GMFP: global mean field power; HS: healthy subjects; LICI: long-interval intracortical inhibition; M1: primary motor cortex; RMT: resting motor threshold; SAI: short-latency afferent inhibition; SICI: short-interval intracortical inhibition; TEP: TMS-evoked potential; TS: test stimulus.

P60. Specifically, SICI reduced the amplitude of both components, while ICF amplified them. The N100 was shown to be increased following both protocols. The bidirectional change in P60 amplitude was further confirmed for both M1 and DLPFC (Cash et al., 2017). Finally, age-related differences in SICI and ICF over DLPFC were also demonstrated recently (Noda et al., 2017b), where older adults (>60 yrs), in comparison with younger adults (<60 yrs), displayed less SICI-related inhibition of the N100 TEP component and less ICF-related potentiation of the N45 TEP component. This suggests that paired-pulse TMS-EEG protocols may be sensitive to assess normal neural aging processes and could potentially help characterize normal versus pathological aging.

5.1.4. Short latency afferent inhibition (SAI)

The combination of median nerve electrical stimulation with TMS leads to MEP suppression when the median stimulation precedes a TS applied to M1 at ISIs of 20–25 ms resulting in so-called short latency afferent inhibition (SAI) (Tokimura et al., 2000). SAI over M1 has been mainly related to cholinergic and GABAAergic circuits (Ziemann et al., 2015).

Bikmullina and colleagues were the first to assess correlates of SAI using TMS–EEG (Bikmullina et al., 2009). Their findings point towards a reduction of the N100, after the application of the SAI protocol over M1, which correlated with the reduction in MEP amplitude. A similar reduction of N100 amplitude was found in another study, which was accompanied by a P60 attenuation and a decrease of the ERSP in the beta band (Ferreri et al., 2012). In another study, SAI was associated with a modulation of the N100 component correlating with MEP suppression, but an increase rather than a decrease of its amplitude was observed (Noda et al., 2016). In addition, the possibility to record SAI in the DLPFC by EEG was explored. Findings showed that it is possible to modulate frontal TEP power when a ISI of N20 + 4 ms was used, manifesting in a decrease of P60 and increase of N100 amplitudes over frontal regions (Noda et al., 2016).

5.1.5. Summary of findings in healthy subjects

Although the use of concurrent TMS and EEG to assess paired-pulse TMS protocols is recent, the available electrophysiological markers of cortical reactivity in TMS-EEG applications can be deployed allowing one to study cortical inhibition/excitation mechanisms in more depth. Combining these paradigms with TMS–EEG offers the unique possibility to investigate the effect of paired-pulse protocols, known to reflect the activity of specific neurotransmitters, on cortical activity in motor and non-motor areas. Importantly, it enables a direct assessment of excitatory and inhibitory mechanisms while bypassing spinal-cord excitability, which is known to influence MEP measurements. On the other hand, more studies are needed to consolidate the currently available findings, and to clarify to what extent the effects of paired-pulse TMS–EEG are equivalent, complementary or different to the well-established paired-pulse TMS–EMG protocols.

5.2. Pharmacology of TMS–EEG

Pharmaco-TMS has greatly contributed to the development of TMS by helping to identify the underlying mechanisms of the TMS–EMG measures and developing indexes of different neurotransmitter activity in M1 that can be translated in clinical practice. In combination with pharmacological interventions, TMS–EEG also holds the potential to study the impact of specific drugs on paired-pulse protocols applied within and outside of M1, as well as to better understand the underlying mechanisms of specific aspects of TMS-evoked EEG activity, such as TMS-locked cortical oscillations and TEP components. Typical pharmaco-TMS-EEG experimental protocols follow a pseudo-randomized, placebo-controlled, crossover and double-blind design where TEPs are recorded before and after the intake of drugs with a well-known and specific mode of action. The results of the reviewed articles are summarized in Table 2.

5.2.1. Gabaergic activity

Four pharmacological TMS-EEG studies involved the assessment of GABAA and GABAB receptors using single pulse TMS protocols. Premoli and colleagues (Premoli et al., 2014a), compared the effect of alprazolam (α1, α2, α3, and α5 subunits of GABAARs), zolpidem (α1-subunit of GABAARs), diazepam (GABAAR agonist) and baclofen (GABABR agonist) on single pulse TEPs. Alprazolam, zolpidem and diazepam increased the N45 amplitude over contralateral motor areas. This result strongly suggested that activity at α1-GABAARs contributed to the N45 component. In line with this result, a novel competitive selective antagonist of the extrasynaptic α5-GABAAR, named S44819, was shown to decrease the N45 amplitude (Darmani et al., 2016), indicating that tonic inhibition mediated by α5-GABAAR may also contribute to the N45 potential.

Apart for the modulation of the N45, Premoli and colleagues (Premoli et al., 2014a) also showed a bidirectional modulation of the N100, with a decrease by GABAARs agonists (alprazolam and diazepam), and an increase by the GABABR agonist baclofen. This important finding corroborated a large body of indirect evidence, which related the N100 TEP to slow inhibitory processes mediated by GABABRs (Nikulin et al., 2003; Bruckmann et al., 2012; Farzan et al., 2013; Casula et al., 2014).

Knowing that GABAergic activity is critical to the production and mediation of oscillatory activity in the human brain, Premoli et al. (2017) reanalyzed the data collected in their previous experiments (Premoli et al. 2014a) to investigate the effect of GABAergic activity on induced and evoked cortical oscillations. Findings suggest that early synchronization and late desynchronization of induced oscillations may be mediated by separate inhibitory mechanisms. As such, early alpha-band synchronization was increased by a GABAAR-mediated drive (zolpidem, diazepam and alprazolam) and decreased by GABABR-mediated activity (baclofen), whereas both GABAAR- and GABABR-activity increased late beta-band desynchronization. Finally, the GABABR agonist baclofen increased late alpha-band desynchronization.

Three studies assessed the effects GABAergic drugs on paired-pulse protocols. Premoli and colleagues investigated the effect of LICI on GABABR- and GABAAR-mediated cortical inhibition (Premoli et al., 2014b). Baclofen was shown to enhance the inhibitory effect of LICI on the P180 TEP component, whereas diazepam decreased the amplitude of the P180 and N100 components (Premoli et al., 2014b). In support of these findings, Salavati and collaborators recently shown that baclofen enhances the inhibitory effect of LICI in the DLPFC, as measured by cortical evoked activity (Salavati et al., 2018b). Finally, the effect of diazepam and baclofen on SICI was also recently investigated in M1 and showed similar bidirectional modulation, with an increase of the inhibitory effect of LICI on the N100 component following the intake of baclofen, and decrease of N100 amplitude following the intake of diazepam (Premoli et al., 2018). Altogether, these studies provide additional evidence for a tight control of GABABR-mediated neurotransmission by GABAAR-mediated activity (Irlbacher et al., 2007; Palmer et al., 2013; Premoli et al., 2014b).

5.2.2. Other pharmacological interventions

The contribution of other neurotransmitters on LICI was also recently assessed by the administration of L-DOPA—a precursor of dopamine, dextromethorphan—an NMDA receptor antagonist, and rivastigmine—an acetylcholinesterase inhibitor (Salavati et al., 2018b). In addition to the effect of baclofen on LICI, rivastig-

Table 2
Pharmacology of TMS–EEG.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Ferrarelli et al. (2010)	11 HS	Right Premotor Cortex (BA6) and more anterior cortical area (BA8)	64 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 120 V/m) Neuronavigation	Connectivity (SCS, SCD) Full consciousness (level 5 of the OAA/S) and during midazolam[1]-induced (0.1 to 0.2 mg/kg) deep unresponsiveness (level 1 OAA/S)	(1) During wakefulness TMS triggered responses in multiple cortical areas lasting for >30 ms (2) During midazolam-induced LOC, TMS-evoked activity was local and of shorter duration
Premoli et al. (2014a)	22 HS 19 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 100% RMT)	TEPs Part 1: Before/after oral dose of alprazolam[2] (1 mg), zolpidem[3] (10 mg) Part 2: Before/after oral intake of diazepam[4] (20 mg) and baclofen[5] (50 mg)	(1) Alprazolam and zolpidem: ↑N45. (2) Alprazolam: ↓ N100 (3) Diazepam: ↑ N45 and ↓N100 (4) GABAB agonist baclofen: ↑N100
Premoli et al. (2014b)	19 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single/paired pulse (monophasic, 100% RMT) ISI: 100 ms	TEPs Before/after single oral dose of diazepam[4] (20 mg) and baclofen[5] (50 mg)	(1) LICI at baseline (i.e. pre-drug intake) characterized by ↓ P25, N45, N100 and P180; and ↑ P70 (2) Baclofen: trend towards the ↑ LICI of the N45 and N100, and significantly ↑ LICI of the P180. (3) Diazepam: ↓ LICI of late potentials (i.e. N100, P180), without having an effect on LICI of earlier (i.e. P25, N45 and P70) potentials
Sarasso et al. (2015)	18 HS (6 per cond.)	Left superior frontal (BA6; n = 3) and superior parietal (BA7; n = 3)	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 110 V/m) Neuronavigation	GMFP Cumulated cortical sources (space and time) PCI Before/ after intravenous dose of: propofol[6] (6ug/ml), xenon[7] (2–3 mg/kg) ketamine[8] (0.05ug/kg/min)	(1) Propofol ↓ GMFP, ↓ cumulated current sources, ↓ PCI (2) Xenon ↑ GMFP, ↑ cumulated current sources, ↓ PCI (3) Ketamine ↓ GMFP, ↔ cumulated current sources, ↔ PCI as compared to wakefulness
Premoli et al. (2016)	15 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 100% RMT)	TEPs Before/after oral dose of lamotrigine[9] (300 mg) and levetiracetam[10] (3,000 mg)	(1) Both AEDs ↑N45 and ↓P180
Darmani et al. (2016)	18 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (monophasic) 100% RMT	TEPs Before/after oral dose of *S44819*[11] (50 and 100 mg)	(1) A dose of 100 mg, but not 50 mg, of S44819 ↓N45. (2) The peak serum concentration of 100 mg S44819 correlated directly with the decrease in N45 amplitude (3) SICI (EMG), and other components of the TMS-evoked EEG response remained unaffected
Premoli et al. (2017)	22 HS 19 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 100% RMT)	Cortical oscillations Part 1: Before/ after oral dose of alprazolam[2] (1 mg), zolpidem[3] (10 mg) Part 2: Before/ after oral dose of diazepam[4] (20 mg) and baclofen[5] (50 mg)	(1) Diazepam and Zolpidem, trend for Alprazolam: early (30–200 ms) ↑ alpha band synchronization in the sensorimotor cortex (2) Alprazolam, Diazepam and Baclofen: ↑ late (200–400 ms) beta band desynchronization over frontal/parietal (3) Baclofen: ↑ late (200–400 ms) alpha band desynchronization over sensorimotor cortex
Salavati et al. (2018b)	12 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single/paired pulse (monophasic, 1 mV) ISI: 100 ms Neuronavigation	TEPs (CEA) Before/after single oral dose of baclofen[5] (50 mg), L-DOPA[12] (100 mg), dextromethorphan[13] (150 mg) and rivastigmine[14] (3 mg)	(1) Baclofen: ↑ LICI related CEA (2) Rivastigmine: ↓ LICI related CEA (3) Trend towards ↑ LICI related CEA after L-DOPA (4) No effect for dextromethorphan
Salavati et al. (2018a)	12 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single pulse (monophasic, 1 mV) Neuronavigation	TEPs (CEA) Pre and 0, 17, 34 and 60 min post PAS25 applied over DLPFC Oral dose of baclofen[5] (50 mg), L-	(1) L-DOPA and rivastigmine: ↑ PAS related potentiation of CEA (2) Dextromethorphan: ↓ PAS related potentiation of CEA

(*continued on next page*)

Table 2 (*continued*)

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
					DOPA[12] (100 mg), dextromethorphan[13] (150 mg) and rivastigmine[14] (3 mg) administered before Pre-PAS	(3) No effect for baclofen compared to placebo
Premoli et al. (2018)	16 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single/paired pulse (monophasic, 70 and 100% RMT) ISI: 2 ms	TEPs Before/ after oral dose of diazepam[4] (20 mg) and baclofen[5] (50 mg)	(1) Prior to drug: SICI induced ↓ N100 and P180 (2) Diazepam: ↓ SICI N100 over right frontal regions (3) Baclofen: ↑ SICI N100 over bilateral frontal regions

Legend: AEDs: antiepileptic drugs; CEA: cortical evoked activity; DR: dopamine receptor; GABAAR: GABAA receptor; GABABR: GABAB receptor; ISI: interstimulus interval; HS: healthy subjects; LICI: long-interval intracortical inhibition; m/nAChR: muscarinic/nicotinergic acetylcholine receptor; NMDAR: NMDA receptor; M1: primary motor cortex; OAA/S: observer's assessment of alertness/sedation; RMT: resting motor threshold; SCD: significant current density; SCS: significant current scattering; TEP: TMS-evoked potential; VGSC: voltage-gated sodium channels./Mode of actions.

1 Benzodiazepine mediated by GABAAR.
2 GABAAR agonist (α1, α2, α3, and α5 subunits).
3 GABAAR agonist (α1 subunit).
4 GABAAR agonist.
5 GABABR agonist.
6 GABAAR agonist.
7 NMDAR antagonist;
8 NMDAR antagonist.
9 VGSC blocker.
10 Binds to synaptic vesicle protein 2A.
11 Novel competitive selective antagonist of the α5-GABAAR.
12 DR agonist.
13 NMDAR antagonist.
14 Cholinesterase inhibitor, m/nAChR stimulation.

mine was shown to decrease the inhibitory effect of LICI on cortical evoked activity, suggesting that it may help reduce abnormally elevated cortical inhibition (Kuo et al., 2007). L-DOPA showed a non-significant trend towards increased LICI inhibition, while dextromethorphan did not modulate LICI.

In a subsequent study conducted by this research group, the modulatory effect of the same pharmacological agents on PAS-induced DLPFC plasticity was explored (Salavati et al., 2018a). L-DOPA and rivastigmine enhanced the PAS-related potentiation of cortical evoked activity, suggesting that both acetylcholine and dopaminergic modulators can increase DLPFC neuroplasticity. Conversely, the NMDAR antagonist dextromethorphan was found to inhibit the potentiation effect of PAS on DLPFC cortical evoked activity. This study highlights the potential of pharmaco-TMS–EEG to study pharmacological modulation of DLPFC neuroplasticity in humans.

A recent study also assessed the effects of the two most prescribed anti-epileptic drugs (AEDs), *i.e.*, lamotrigine and levetiracetam, on TEPs (Premoli et al., 2016). Independently of their differential molecular mechanisms, they both increased the amplitude of the N45 and suppressed the P180 component at the system level. These TMS–EEG findings may indicate candidate predictive markers of treatment response in patients on monotherapy with lamotrigine or levetiracetam.

Finally, two studies assessed the effect of drug-induced loss of consciousness (LOC) on TMS-EEG activity. Ferrarelli et al. (Ferrarelli et al., 2010) used midazolam, a classical benzodiazepine, to induce loss of consciousness (LOC) in healthy volunteers. Midazolam increased amplitudes of early TEPs and reduced TEP amplitudes at longer latencies ($\geq$100 ms), suggesting a breakdown in long-range cortico-cortical effective connectivity. TMS–EEG was also recently used to test the effects of three different anesthetics (Sarasso et al., 2015). Propofol (potentiates GABA neurotransmission) and xenon (potentiates conductance of K+ channels, NMDA receptor antagonist) were characterized by a local and global low-complexity TMS-evoked EEG response. Ketamine (NMDA receptor antagonist), on the other hand, which is associated with a vivid dream experience, produced a complex spatio-temporal signal similar to wakefulness. These findings demonstrate that the TMS-evoked EEG responses are highly sensitive to changes in level of consciousness.

5.2.3. Summary of findings on pharmacology of TMS-EEG

Despite its early days of use, pharmaco- TMS–EEG interventions have already provided promising results and have opened new avenues of investigation. Studies have provided insight into the mechanism of action of some well-known TMS protocols, such as LICI and SICI, and helped characterize the involvement of neurotransmitter's activity in TMS-EEG measures, such as TEPs and cortical oscillations. Importantly, these studies have suggested that TMS-EEG may have a different sensitivity than TMS-EMG with regards to measures of inhibition, such as LICI and SICI, and/or may reflect different mechanisms associated with these measures. In addition, results from reviewed studies suggest that the same TEP component can be modulated by different drugs, again highlighting a potential differential sensitivity of pharmaco-TMS-EEG in comparison with TMS-EMG studies. Future studies are needed to replicate findings and to explore if pharmaco-TMS-EEG can help better characterize TEPs outside of motor regions.

5.3. TMS–EEG and non-invasive brain stimulation protocols to study plasticity

Different non-invasive transcranial brain stimulation (NTBS) protocols that modulate cortical circuits through plasticity-like effects have been developed. These include regular repetitive tran-

scranial magnetic stimulation (rTMS), theta-burst stimulation (TBS), paired-associative stimulation (PAS) and transcranial direct current stimulation (tDCS). As described above, however, evaluation of these plasticity-inducing paradigms has been largely restricted to M1 because of the lack of an objective and reliable index of cortical excitability in non-motor areas. As a consequence, it remains to be determined if expected effects of these standard NTBS protocols developed over M1 translated to non-motor regions.

Despite this lack of reliable measures outside of motor regions, TMS and tDCS paradigms have rapidly been employed in clinical populations to modulate excitability of regions that are thought to be involved in the pathophysiology of specific disorders. A good example is major depression, for which the U.S. Food and Drug Administration (FDA) has approved treatment with rTMS in individuals that have not responded or who cannot tolerate pharmacotherapy. While effects of stimulation have largely been assessed via clinical rating scales, neuroimaging methods such as fMRI and resting-state EEG (see (Thut and Pascual-Leone, 2010)) have been used to study the neuronal effects underlying stimulation, which has contributed to a better understanding of the NTBS-induced effects. Nevertheless, our understanding of rTMS effects over non-motor cortical regions remains poor.

The recent development of TMS–EEG offers new insights into the NTBS-effects on motor and motor cortical regions. Apart from providing an index of induced changes in local intracortical excitatory and inhibitory circuits, it also offers the possibility to capture different aspects of cortical plastic reorganization, such as changes in connectivity patterns and in the generation of oscillatory activity (Chung et al., 2015). In the present section, recent evidence on the use of TMS–EEG in conjunction with different stimulation protocols will be concisely summarized (see (Chung et al., 2015), for a review). The results from the reviewed publications are summarized in Table 3.

5.3.1. Regular repetitive transcranial magnetic stimulation

Repetitive TMS (rTMS) involves the application of trains of magnetic pulses at various frequencies. When they are applied using an appropriate temporal pattern, duration and intensity, modifications in synaptic efficacy that outlast the period of stimulation are expected. Together with synaptic activity modulation, rTMS is thought to produce more complex changes including gene activation/regulation, de novo protein expression, morphological changes, and glial function modulation (Noda et al., 2015b; Cirillo et al., 2017). Conventional rTMS paradigms usually involve suprathreshold pulses and high numbers of stimuli (10–25 min duration). When applied over motor regions, there is a general consensus that low frequencies ($\leq$1 Hz) mainly suppress, while higher frequencies (5–20 Hz) facilitate MEPs (Ziemann et al., 2008; Rossini et al., 2015).

Early in the development of TMS–EEG, the technique was used to assess the effect of rTMS applied to M1 on cortical excitability. One of the main assumptions is that the mechanisms underlying the modulatory impact of rTMS in human cortex are similar to those of long-term potentiation (LTP) and depression (LTD) observed in animal studies, which can be quantified via changes in the response amplitude to electrical stimulation using extracellular electrodes (Madison et al., 1991; Cooke and Bliss, 2006). As such, early studies used TMS–EEG to assess the analogy of rTMS outcomes to LTP-like effects. Esser and colleagues (Esser et al., 2006) found that 5 Hz rTMS applied to M1 increased the amplitude of TMS-evoked EEG responses in bilateral premotor cortices, whereas M1 excitability remained unchanged. This provides evidence for a direct modulation of closely interconnected motor regions following rTMS.

Regarding low-frequency rTMS, it was shown that 0.6 Hz rTMS can modulate M1 excitability, as indexed by a reduction in the amplitude of the N45 component, when it is applied over M1 but not the dorsal premotor cortex (Van Der Werf and Paus, 2006). Interestingly, this M1-specific effect on cortical excitability was observed despite no significant group effect on MEPs, suggesting that TMS–EEG is a sensitive tool to assess rTMS-induced changes in cortical excitability. Another study assessed low frequency (1 Hz) rTMS on M1 and the premotor cortex, but specifically assessed the after-effects on M1 short-latency TEPs, i.e., the P5–N8 complex, which was previously shown to be modulated *during* rTMS (Veniero et al., 2010). Their results showed no significant group effect on the early components, or on MEPs (Veniero et al., 2012). However, single-subject analyses showed a reduction of the P5–N8 complex in the majority of participants after rTMS over the premotor cortex, suggesting that these early TEPs components can be sensitive to changes in cortical excitability induced by low frequency rTMS. More recently, (Casula et al., 2014) assessed the effects of 1 Hz rTMS applied to M1 compared to a control condition where stimulation was applied to the primary visual cortex (V1). Results suggested the presence of a specific modulation of M1 GABAB-ergic transmission, with increased amplitude of the P60 and N100 components following M1 rTMS only. No significant correlation between MEP and TEP changes were observed, which the authors hypothesized to be due to the discrepancy in the sensitivity between both measures.

5.3.2. Theta-burst stimulation

Theta-burst stimulation (TBS) is a repetitive TMS protocol that uses short bursts (usually triplets at 30–50 Hz) of subthreshold pulses applied at a carrier frequency of 5 Hz (Huang et al., 2005; Suppa et al., 2016). This protocol is based on animal studies that have employed theta-burst paradigms to induce LTP and LTD (Larson et al., 1986; Hess and Donoghue, 1996). The direction of the induced changes on brain excitability depends on the temporal pattern of the bursts. When applied in an intermittent fashion (intermittent TBS or iTBS; 2 s TBS trains every 10 s for a total of 190 s), increases in corticospinal excitability are expected over motor regions. Inversely, when applied a continuously (continuous TBS or cTBS; for a total of 20–40 s), inhibition is observed.

Vernet et al. (2013) assessed the effect of cTBS applied to M1 on TEPs and showed a decrease in P30 amplitude, which was linked to suppression of MEPs. In addition, cTBS also increased TMS-evoked theta and alpha oscillations, while it decreased beta oscillations. More recently, Rocchi and colleagues showed decreased LMFP and reduced power in theta, delta and gamma oscillations after cTBS of M1 (Rocchi et al., 2018). Reduced synchronization of activity was also observed following cTBS in the delta and theta frequency range. Although there are some discrepancies in results, both studies suggest a decrease of cortical excitability following cTBS of M1. Regarding iTBS, only study assessed the its effect on M1 TEPs and found no effect on N15-P30 amplitude (Gedankien et al., 2017).

Two studies have investigated the impact of TBS applied to the lateral cerebellum on TMS–EEG-determined M1 reactivity. The cerebellum has been an increasingly studied target for modulating the cerebello-thalamo-cortical pathway because of its involvement in several neurological disorders such as dystonia and Parkinson's disease (Tremblay et al., 2016). Harrington and Hammond-Tooke (Harrington and Hammond-Tooke, 2015) investigated the effect of a modified version of cerebellar TBS using the frequency of 30 Hz (cTBS, iTBS or sham) on M1 excitability. Cerebellar iTBS increased the N100 amplitude assessed over M1 while no change in MEP amplitude was obtained. cTBS induced a reduction in both N100 and MEP amplitudes. This bidirectional modulation of the N100 amplitude indicates that cerebellar TBS can directly act on the cerebello-thalamo-cortical networks and that TMS–EEG may be a more sensitive method than TMS–EMG to assess those

Table 3
Non-invasive brain stimulation protocols in healthy individuals.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Repetitive transcranial magnetic stimulation						
Esser et al. (2006)	7 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90% RMT) Neuronavigation	TEPs (GMFP, topography), Source localization Pre and post: 1 session of real and sham 5 Hz rTMS	(1) Bilateral premotor cortex ↑in TEP amplitude and GMFP post rTMS (2) Source localization in single subject: local M1 activity followed by ipsilateral premotor cortex activation
Van Der Werf and Paus (2006)	12 HS	Left M1 Left PMd	9 channels Sampling rate: 1450 Hz	Single pulse (monophasic, 115% RMT) Neuronavigation	TEPs, oscillations Pre and 0, 10, 20, 30 min post 0.6 Hz rTMS over M1 and PMd	(1) M1 rTMS: ↑ amplitude of N45 (2) PMd rTMS: ↓ N100 amplitude over M1 (3) M1 and PMd rTMS: ↓ theta power
Veniero et al. (2012)	13 HS	Left M1	70 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 110% RMT) Neuronavigation	Short-latency TEPs Pre/Post 1 Hz rTMS over PMC or M1 (single pulse over M1 only)	(1) no significant group effect on P5-N8 (2) PMC rTMS: ↓P5-N8 amplitude in 6/13 and ↑ in 2/13 participants (3) negative correlation between modulation of the P5-N8 complex and MEP amplitude
Casula et al (2014)	15 HS	Left M1	64 channels Sampling rate: 2048 Hz	Single pulse (biphasic, 120% RMT) Neuronavigation	TEPs (LMFP) Pre and post: 1 Hz rTMS over M1 and V1 (control)	(1) ↑ P60 and N100 amplitude post rTMS (2) ↑ late LMFP post rTMS
Theta burst stimulation						
Vernet et al. (2013)	10 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120% RMT) Neuronavigation	TEPs Synchronization, oscillations Pre and 0, 5, 10, 20, 30, 40, 50, 60 min post cTBS	(1) ↓ P30 amplitude post cTBS reflect MEP suppression (2) ↑ power in beta band and ↓ theta and alpha following cTBS
Harrington and Hammond-Tooke (2015)	16 HS	Left M1	32 channels Sampling rate: 20 kHz	Single pulse (biphasic, 90% RMT)	TEP N100 Pre and post 30 Hz cerebellar iTBS, cTBS and sham applied at 80 and 90% of AMT	(1) iTBS (90% AMT): ↑N100 amplitude vs. sham and cTBS (2) cTBS (80% AMT): ↓N100 amplitude
Casula et al. (2016b)	20 HS	Left M1 Left PPC	32 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 90% RMT) Neuronavigation	TEP (LMFP) Cortical oscillations (ERSP) Pre and post cerebellar iTBS, cTBS and sham	(1) cTBS: ↓ (35–55 ms) followed by ↑ (around 100–200 ms) in TEP amplitude for both PPC and M1 (2) iTBS: ↓ TEP amplitude (around 100–200 ms) for both PPC and M1 (3) In M1, alpha activity ↓ by cTBS, and beta activity ↑ by iTBS
Chung et al. (2017)	10 HS	Left DLPFC	39 channels Sampling rate: 10 kHz	Single/paired pulse (monophasic, 120% RMT) ISI: 100 ms	TEP, cortical inhibition, oscillations Pre and post iTBS, cTBS and sham	(1) iTBS: ↑ N120 amplitude left and right DLPFC, local change in P200, ↑ single pulse and LICI theta power (2) Correlation between change in N120 and LICI theta power (3) cTBS: ↓ theta power after stimulation (not different from sham)
Gedankien et al. (2017)	17 HS	Left M1	61 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120% RMT) Neuronavigation	TEP, GMFP Pre and post iTBS	(1) No change in N15-P30 amplitude after iTBS
Chung et al. (2018b)	16 HS	Left DLPFC	42 channels Sampling rate: 10 kHz	Single pulse (biphasic, 120% RMT)	TEP, oscillations Pre and post iTBS at 50, 75 and 100% of rMT	(1) ↑ N100 amplitude, maximal at 75%rMT (2) ↑ theta power, maximal at 75%rMT
Chung et al. (2018a)	18 HS	Left DLPFC	48 channels Sampling rate: 10 kHz	Single pulse (biphasic, 120% RMT)	TEP, oscillations Pre and post iTBS (1block), iTBS (2blocks, 15 min inter-block), sham	(1) 1 and 2 blocks of iTBS: ↑ N100 and P200 amplitude
Rocchi et al. (2018)	13 HS	Left M1	62 channels Sampling rate: 2048 Hz	Single pulse (monophasic, 1 mV)	LMFP, ERSP, ITPC Pre and post cTBS 2 sessions: 1 mV intensity, and half-maximum MEP intensity	(1) cTBS ↓ LMFP (trend); ↓ ERSP in delta, theta and gamma band, and; ↓ ITPC in delta and theta band
Transcranial direct current stimulation						
Pellicciari et al. (2013)	16 HS	Left M1	32 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 110% RMT) Neuronavigation	LMFP Pre, post, and 30 min post anodal (1 mA, 13 min) and cathodal tDCS	(1) Anodal tDCS: ↑cortical reactivity in both M1s lasting up to 265 ms (2) Cathodal tDCS: ↓cortical reactivity in left M1 and ↑ cortical reactivity in right M1 (3) No significant correlation between MEPs and LMFP
Romero Lauro et al. (2014)	14 HS	Left PPC	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 106 V/m) Neuronavigation	GMFP, LMFP Pre, during and post anodal (0.75 mA, 15 min) and sham tDCS over right PPC	(1) ↑ GMFP during and post tDCS (0–100 ms) (2) ↑ LMFP in bilateral frontal and parietal during and post tDCS, and ↑ in right temporal LMFP during tDCS

Table 3 (*continued*)

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Hill et al. (2017)	19 HS	Left DLPFC	36 channels Sampling rate: 10 kHz	Single pulse (monophasic, 110% RMT) Neuronavigation	TEP, oscillations Pre, 5 min and 30 min post anodal tDCS (1 mA, 20 min): (1) high-definition (HD-tDCS, F3/FP1-FZ-C3-F7), (2) bipolar (BP-tDCS, F3/Fp2), (3) sham	(1) ↑ P60 amplitude over left DLPFC 5 min post BP-tDCS (2) ↑ P60 amplitude over bilateral fronto-central and parieto-occipital regions following HD-tDCS (3) ↓ beta and gamma oscillatory power over parieto-occipital regions 30 min post-HD-tDCS
Gordon et al. (2018)	22 HS	Left and Right DLPFC	64 channels Sampling rate: 5000Hz	Single pulse (biphasic, 120% RMT) Neuronavigation	TEP, oscillations Pre and post 14 min of: 1) 1.5 mA left-anode/right-cathode; 2) 1.5 mA left-cathode/right-anode; 3) 0.5 mA, left-anode/right-cathode; 4) 1.5 mA left-anode/right deltoid muscle; 5) sham	(1) 1.5 mA left-anode/right-cathode: ↓ N120 over parietal cortex (2) Conditions 1, 3, 4 (left-anode): ↓ power of induced theta and gamma oscillations
Varoli et al. (2018)	15 HS	Right PPC	60 channels Sampling rate: 1450 Hz	Single pulse (bihasic, 100 V/m) Neuronavigation	GMFP, LMFP SCD Pre, during, post (0 and 10 min) 15 min of 0.5 mA cathodal vs sham PPC tDCS	(1) No effect of cathodal tDCS during or after stimulation on all TMS-EEG measures
Paired associative stimulation						
Huber et al. (2008)	19 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90% RMT) Neuronavigation	TEPs (GMFP) Pre and post M1 PAS25, PAS10 or sham	(1) PAS25: ↑ GMFP ispi- and contra-lateral to the stimulation site (2) PAS10: ↓ GMFP at stimulation site
Rajji et al. (2013)	15 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single pulse (monophasic, 1 mV) Neuronavigation	TEPs-mean evoked cortical activity Cortical oscillations Pre and 0, 15, 30 min post DLPFC PAS25 and PAS100 (sham)	(1) ↑ cortical evoked activity frontal regions (2) ↑power in gamma, theta and delta bands (3) ↑ gamma-theta coupling
Veniero et al. (2013)	13 HS	Left M1 Left PPC	32 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 1 mV) Neuronavigation	TEPS (GMFP) Cortical oscillations Connectivity Pre and post PPC-$M1_{PA}$ + 5 PAS, PPC-$M1_{PA}$ −5 PAS, PPC-$M1_{AP}$ + 5 PAS	(1) PPC-$M1_{PA}$ + 5 PAS: ↑ amplitude of P1 (30 ms) in M1 and ↑coherence in beta band (2) PPC-$M1_{PA}$ −5 PAS: ↑ amplitude of P1 (30 ms) and P4 (180 ms) in M1 and ↑ coherence in alpha band (3) PPC-$M1_{AP}$ + 5 PAS: ↓ amplitude of P1 (30 ms) and P4 (180 ms) in M1 and ↑ coherence in alpha band
Casula et al. (2016a)	14 HS	Left DLPFC Left PPC Left M1	32 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 90 RMT) Neuronavigation	TEP (GMFP) Cortical oscillations Pre and post PF PAS (PPC-DLPFC) and FP PAS (DLPFC-PPC)	(1) DLPFC – FP PAS: ↑ GMFP 112–282 ms, ↑ beta and gamma power (2) DLPFC – PF PAS: ↓ GMFP 112–282 ms, ↓ beta power (non-significant)

Legend: AP: anterior-posterior; BP-tDCS: bipolar transcranial direct current stimulation; cTBS: continuous theta burst stimulation; DLPFC: dorsolateral prefrontal cortex; ERSP: event-related spectral perturbation; FP: fronto-parietal; GMFP: global mean field power; HD-tDCS: high-definition transcranial direct current stimulation; HS: healthy subjects; iTBS: intermittent theta burst stimulation; ITPC: inter-trial phase clustering; LMFP: local mean field power; LICI: long-interval intracortical inhibition; M1: primary motor cortex; PA: posterior-anterior; PAS: paired-associative stimulation; PMd: dorsal premotor cortex; PPC: posterior parietal cortex; RMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; SCD: significant current density; tDCS: transcranial direct current stimulation; TEP: TMS-evoked potential; V1: primary visual cortex.

changes. The after-effects of cerebellar TBS was further studied by Casula and colleagues, alongside after-effects on M1 and a so-called "silent" region, the posterior parietal cortex (PCC), with both M1 and PPC known to be under the influence of cerebellar projections (Casula et al., 2016b). Bidirectional changes in TEP amplitude around 200 ms were observed for both PCC and M1 stimulation, with cTBS leading to increased and iTBS to decreased amplitude, which is consistent with a modulation of inhibitory activity of Purkinje cells in the cerebellum. Over M1, bidirectional changes were also observed in oscillatory activity: iTBS reduced TMS-evoked alpha activity, whereas cTBS enhanced beta activity. Although changes in opposite directions were observed in these two cerebellar TBS studies, they suggest that stimulation of the lateral cerebellum can lead to changes in cortical excitability, most likely related to alterations in interneuronal associated with GABAergic activity. This may occur by activation of local cortical interneurons that are linked through a poly-synaptic pathway to the cerebellum (Daskalakis et al., 2004).

Three recent studies assessed the effect of TBS on DLPFC activity. In a first study, Chung and colleagues (Chung et al., 2017) applied iTBS, cTBS and sham to the left DLPFC and measured the modulatory effect on TEPs, cortical oscillations and cortical inhibition (LICI). Their results suggested the presence of short-term plasticity effects following iTBS, illustrated by an increase in N120 amplitude and theta power, as well as an increase of LICI-related theta power. cTBS only marginally decreased theta power, however this effect was not different from sham. These findings were the first to support the use of TBS to modulate prefrontal cortical reactivity. In two follow-up studies by the same group, Chung et al. assessed the effects of three different intensities of iTBS (Chung et al., 2018b), as well as one versus two blocks of iTBS on TEPs and cortical oscillations (Chung et al., 2018a). They reported a

u-shape effect of intensities on prefrontal plasticity, with 75% of RMT inducing the strongest modulatory effect, in comparison with 50 and 100% of RMT (Chung et al., 2018b). Specifically, iTBS induced an increase in N100 amplitude and oscillatory theta-power activity. In addition, a separate study showed no difference between one versus two consecutive blocks of iTBS, whereby both active iTBS sessions increased the amplitude of N100 and P200 (Chung et al., 2018a). Altogether, these studies provided evidence for an effect of iTBS on DLPFC cortical reactivity, with an increase in N100, P200 and theta power. TMS–EEG provided important insight into the effects of intensity and duration of iTBS applied to the DLPFC.

5.3.3. Transcranial direct current stimulation (tDCS)

Bidirectional changes in M1 corticospinal excitability can also be obtained via transcranial direct current stimulation (tDCS), which involves the application of low-intensity electric currents between two surface electrodes placed over the scalp (Nitsche and Paulus, 2000). The nature of the tDCS-related changes in cortical excitability depends on the polarity of the electrode that is positioned over the target region, as well as on stimulation parameters such as duration and intensity. In general, when the anode is positioned over M1 and the cathode is positioned over the supraorbital region of the contralateral hemisphere, MEP facilitation occurs; when the polarity of the electrodes is reversed, MEP inhibition occurs (Nitsche and Paulus, 2011).

One study used TMS–EEG to investigate tDCS after-effects on motor regions. Pellicciari and colleagues (Pellicciari et al., 2013) applied anodal and cathodal tDCS to the left M1, and measured immediate and long-term (post 30 min) effects on bilateral M1 cortical reactivity. Their results showed a polarity-specific modulatory effect of tDCS on the targeted (left) M1, with anodal tDCS increasing and cathodal tDCS decreasing LMFP amplitude. In contrast, both stimulation protocols induced an increase in the cortical reactivity of contralateral (right) M1 LMFP amplitude. Changes in MEPs were not correlated to changes in LMFPs, suggesting that TMS–EEG may assess differential aspects of cortical excitability changes following tDCS than TMS–EMG.

Romero Lauro et al. (2014) studied online effects (during tDCS) and offline effects (after tDCS) of anodal tDCS of posterior parietal cortex (PPC) on local activity, as well as on interconnected regions through connectivity analysis. To do so, single pulse TMS was delivered over the left PPC before, during and after 15 min of tDCS applied to the right PPC. Immediate and delayed increases in early TEP components (0–100 ms) were obtained in widespread areas, including bilateral frontal and parietal regions. Specifically, GMFP was increased, and LMFP was increased in bilateral frontal and parietal regions both during and after anodal tDCS. Authors conclude that TMS–EEG is a sensitive measure of the online and offline spreading of activations induced by tDCS. However, caution should be taken when interpreting these results because of the possible confound from volume conduction in the employed connectivity analysis (Bailey et al., 2016). The right PPC was also recently targeted with 15 min of 0.5 mA sham and cathodal tDCS (Varoli et al., 2018). Interestingly, no significant effect was obtained on all measures of TMS-evoked activity during or post-stimulation. This suggests that anodal tDCS may be more consistent in modulating the PPC.

Hill and colleagues (Hill et al., 2017) applied anodal tDCS to the left DLPFC using bipolar (i.e., anode – F3 and cathode – Fp2) and high-definition (i.e., anode – F3 and four cathodes – Fp1, FZ, C3, F7) montages and compared their effects to sham tDCS over the same area. They reported local P60 amplitude increase following both active tDCS protocols, whereas widespread changes in P60 amplitude were additionally observed following high-definition tDCS. Moreover, high-definition tDCS induced a distal and delayed decrease in TMS-evoked beta and gamma oscillatory power over posterior regions. Similarly, Gordon and colleagues (Gordon et al., 2018b) studied four different bipolar tDCS montages (vs. sham) over the DLPFC. Their results showed a decrease of the N120 TEP component following 1.5 mA stimulation using a left/anode and right/cathode montage. Montages that included left anodal stimulation of the DLPFC reduced power of theta and gamma oscillations. These studies illustrate that TMS–EEG is a sensitive tool to assess differential modulation of cortical activity produced by different tDCS parameters, such as electrode montage.

5.3.4. Paired-associative stimulation

Typically, cortical paired-associative stimulation (PAS) entails pairing a suprathreshold electrical stimulus applied to a peripheral nerve (usually, the median nerve) with a suprathreshold TMS pulse applied to contralateral M1 using short ISIs. Adjusting this ISI modulates the effect of the protocol in a way that mirrors the effect seen with animal models of spike-timing-dependent plasticity (STDP), whereby if a pre-synaptic input precedes post-synaptic excitation, synaptic transmission is facilitated, and if post-synaptic excitation precedes a pre-synaptic input, transmission is inhibited. It is generally agreed that ISIs of 21.5–25 ms are facilitatory, consistent with a pre-synaptic input preceding post-synaptic excitation, whilst shorter ISIs (~10 ms) produce an inhibitory effect (Stefan et al., 2000; Carson and Kennedy, 2013; Suppa et al., 2017).

Huber et al. (2008) assessed the effects of PAS applied at ISIs of 10 and 25 ms on M1 TMS-evoked EEG activity. While PAS_{25ms} increased cortical excitability, as indexed by GMFP and MEP amplitudes, in regions both ipsi- and contralateral to the stimulation site, PAS_{10ms} decreased GMFP and MEP amplitudes at the stimulation site. Changes recorded via TMS–EEG and TMS–EMG were characterized by a large inter-subject variability. In addition, because of recent evidence in the relationship between sleep and neural plasticity, the authors were interested in assessing if changes in TMS-evoked cortical EEG responses induced by PAS could predict changes in sleep slow-wave activity. Individuals who showed increases in global TEP amplitudes following PAS also showed subsequent local increases in sleep slow-wave activity and conversely, individuals in which PAS produced reductions in global TEP amplitudes displayed decreases in sleep slow-wave activity. This is hence thought to reflect the ability of PAS to modulate cortical plasticity, and the ability of the TMS–EEG to capture these changes.

Recently, attempts have been made in using the principle of STDP shown for M1 PAS in two other cortical regions of the brain. For example, Hebbian and anti-Hebbian-like phenomena were recently shown by pairing posterior parietal cortex (PPC)- and M1-TMS at different intervals (Koch et al., 2013). This protocol was first tested with TMS and EMG, where MEP depression was observed when PPC stimulation preceded M1 stimulation and potentiation when M1 stimulation preceded PPC stimulation by 5- and 20-ms. The same group of researchers (Veniero et al., 2013) further studied the effects of this novel paradigm by using TMS–EEG to measure PCC–M1 PAS-induced oscillations and connectivity changes. They obtained PAS-induced changes in the amplitude of early and late TEPs over M1, suggestive of local cortical excitability modulation. In addition, TMS–EEG allowed to highlight the presence of connectivity changes between M1 and PPC across different frequency bands, which could be indicative of changes in cell-assembly communication underlying associative learning (Veniero et al., 2013). Another group of researchers investigated the scope of employing PAS to induce potentiation of DLPFC activity, whereby median nerve stimulation was paired with DLPFC stimulation at an ISI of 24 ms (Rajji et al., 2013). This design choice was based on the following assumptions: (1) median nerve stimu-

lation can produce somatosensory evoked potentials over contralateral frontal regions at the latency of 24 ms, and (2) rich anatomical connections are found between somatosensory and prefrontal areas (Rajji et al., 2013). Increases were found in CEA and cortical oscillations following DLPFC PAS. Notably, the potentiation of CEA was spatially specific, i.e., localized within the stimulated DLPFC region, and frequency-specific, i.e., associated with robust potentiation of TMS-evoked gamma and theta activity. Increased theta-phase–gamma-amplitude coupling was also obtained, which is thought to be a neurophysiological index of DLPFC function. The authors suggest that these results are consistent with a possible synaptic potentiation effect associated with DLPFC PAS.

Capitalizing on the development of TMS–EEG measures allowing for quantification of plasticity induction in non-motor regions, more recently Casula et al. (2016a) investigated the presence of STDP within the fronto-parietal network by applying the PAS protocol over DLPFC and PPC. Specifically, they applied two different conditions of PAS: (1) FP (fronto-parietal) PAS where DLPFC stimulation was followed by PPC stimulation at an interval of 10 ms (100 pairs, 0.2 Hz) and inversely, (2) PF (parieto-frontal) PAS where DLPFC stimulation was followed by PPC stimulation. Bidirectional changes of TMS-evoked cortical activity and high-frequency oscillatory activity were highlighted after that DLPFC stimulation was followed/preceded by PPC stimulation. For instance, PAS induced opposite changes on TMS-evoked potential amplitudes (GMFP) and power in the beta and gamma bands at the level of the DLPFC, where FP PAS increased activity and PF PAS reduced it. These effects were specific to the DLPFC, as no changes in TMS–evoked potentials and cortical oscillations were observed at the level of M1 and PPC. These findings provided a physiological demonstration that STDP can be evoked bidirectionally in the human DLPFC, with possible implications in the treatment of several cognitive and psychiatric disorders involving DLPFC dysfunction.

5.3.5. Summary of findings on plasticity

TMS–EEG studies to evaluate the effects of NTBS of different stimulation protocols remain limited in number. However, they have provided strong evidence of the unique contribution that concurrent TMS and EEG can make in the study of the modulatory impact of TMS not only on local cortical circuits, but also on distant regions and cortical network activity. They also provide evidence for TMS–EEG as a valuable complement to the investigation of corticospinal activity with TMS–EMG. For instance, such studies have provided further evidence for the modulation of M1 GABAergic activity by rTMS, and for modulation of nearby motor regions such as the premotor cortex. rTMS outcomes remain to be assessed in more depth with TMS–EEG in non-motor areas. This aspect would be highly relevant to better understand how rTMS can induce behavioral changes, and for optimal targeting of specific intracortical circuits in regions such as the DLPFC. Regarding TBS, motor networks were studied mostly, with the exception of three recent studies that investigated the DLPFC, providing insight into neuromodulatory effect of TBS on cortical activity. Effects of tDCS in non-motor region were assessed in two studies; these findings have proven highly useful in improving our understanding of tDCS after-affects, as well as in the understanding of online effects and differential effects of specific electrode montages. Finally, TMS–EEG has allowed for the development of novel PAS paradigms involving non-motor regions, suggesting that it may allow for expanding the range of stimulation protocols available for inducing LTD/LTP-like effects in humans. A better understanding of the effects of those methods on TMS-related EEG biomarkers could help to further the use of TMS–EEG as an outcome measure of TMS NTBS treatments in clinical disorders.

6. Clinical applications

6.1. Psychiatry

Because of the primary involvement of non-motor regions in the psychopathology of psychiatric disorders, and the ability to obtain a neurophysiological readout of treatment effects as well as a measure of neurophysiological underpinnings of disorders, TMS–EEG offers a highly promising potential for clinical applications. TMS combined with EMG has already proven valuable for neurophysiological and therapeutic interventions in many psychiatric disorders (Bunse et al., 2014). However, translation into clinical practice has been limited by restriction to motor regions, which are not closely related to the target regions for therapy (Bunse et al., 2014). Recently, the potential of TMS–EEG for extending TMS excitability measures to the whole cortex has led to a surge of its use in research on participants with mental health disorders. Specifically, TMS–EEG has been used to study clinical neurophysiology with and without treatment in a range of disorders, including schizophrenia, major depression, bipolar disorder, addiction, autism spectrum disorders and attention deficit hyperactivity disorder. The next sections will focus on describing current TMS–EEG applications in psychiatry and will discuss the clinical prospective for each of these psychiatric disorders. The main results of the reviewed studies are summarized in Tables 4–8.

6.1.1. Schizophrenia

Schizophrenia (SCZ) is a psychiatric disorder characterized by positive (e.g., delusions, hallucinations) and negative (e.g., amotivation, social withdrawal) symptoms; it has a lifetime prevalence of 2–3% (van Os and Kapur, 2009). Although the pathophysiology of the disorder remains poorly understood, animal and post-mortem studies suggest the presence of excitatory and inhibitory neuronal dysfunctions, such as reduced function of GABAergic neurons in the DLPFC (Lewis et al., 2005; Veerman et al., 2014). Several studies used TMS–EMG to assess the integrity of both excitation and inhibition in M1 in SCZ converging on altered M1 GABAergic inhibition (see (Radhu et al., 2012; Bunse et al., 2014; Rogasch et al., 2014) for review). Another line of evidence for the implication of GABAergic inhibitory dysfunctions in SCZ arises from the EEG literature which suggests abnormal spontaneous EEG rhythms particularly related to beta and gamma oscillations (Uhlhaas and Singer, 2013). GABAergic inhibitory interneurons have been proposed to be implicated in the generation ($GABA_A$) and modulation ($GABA_B$) of gamma oscillations (Farzan et al., 2010a). Conductivity and connectivity have also been shown to be disrupted, as suggested by TMS–EMG studies (Rogasch et al., 2014) and TMS–fMRI studies (Sale et al., 2015). However, because of the ability to assess effective connectivity in SCZ, TMS–EEG offers a unique tool to further investigate the involvement of altered connectivity.

A spin-off of the development of TMS–EEG is the study of cortical inhibition and excitation in motor and non-motor regions, such as the DLPFC (for recent reviews see (Rogasch et al., 2014) and (Kaskie and Ferrarelli, 2018)). To date, the majority of studies have used TMS–EEG to shed light on the neurophysiological signatures of SCZ, while no study has yet assessed the effects of a specific treatment on TMS–EEG measures (see Table 4). Collectively, the reviewed research in this field can be divided in a few central topics, including the study of: frontal cortical inhibition using paired-pulse TMS; single pulse TMS-induced EEG oscillations, including the natural frequencies in motor and frontal regions; TMS-related EEG measures of cortical excitability and connectivity; and task-related activity using TMS–EEG.

Study of frontal cortical inhibition using paired-pulse TMS: Four studies assessed inhibition in prefrontal cortex of people with

Table 4
Schizophrenia.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Ferrarelli et al. (2008)	16 SCZ 14 HS	Right premotor cortex	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120 V/m) Neuronavigation	Gamma oscillations	(1) ↓ amplitude and synchronisation of gamma oscillations in fronto-central electrodes (2) ↓ propagation of gamma oscillations
Levit-Binnun et al. (2010)	8 SCZ 6 HS	Cz Sham 1: 2 cm above Cz Sham 2: 40 cm away from subject	64 channels Sampling rate: 512 Hz	Single pulse (biphasic, 70% MSO)	TEPs	(1) ↓ amplitude of GMFP (57 ms) (2) ↓ frontal negativity and centro-parietal positivity
Farzan et al. (2010a)	14 SCZ 14 Bipolar 14 HS (age/ education matched)	Left M1 Left DLPFC Sham (coil angled at 90degree)	64 channels Sampling rate: 20 kHz	Single/paired pulse (monophasic, 1 mV) LICI (ISI: 100 ms) Neuronavigation	Cortical inhibition in 5 frequency bands	(1) SCZ only: ↓cortical inhibition in the gamma band in prefrontal regions
Ferrarelli et al. (2012)	20 SCZ 20 HS (age-matched)	Posterior parietal cortex Motor cortex Premotor cortex Prefrontal cortex	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120 V/m – 110–115% of RMT) Neuronavigation	TMS-evoked oscillatory activity (ERSP) TMS-evoked synchronisation (ITC) Natural Frequency	(1) Slowing in natural frequency of prefrontal region (2) ↓ in ERSP and synchronization of beta/gamma oscillations in prefrontal sites
Frantseva et al. (2014)	16 SCZ 16 HS	Left M1 Sham (coil angled at 90degree)	64 channels Sampling rate: 20 kHz	Single pulse (monophasic, 1 mV)	Connectivity (time, space, frequency analysis)	(1) Excessive propagation of signal in the time and space (2) ↑ oscillatory activity in delta (ipsilateral frontal and temporoparietal, bilateral occipital and parietal), beta-gamma (bilateral motor cortex and fronto-temporo-parietal).
Canali et al. (2015)	12 SCZ 12 MDD 12 BPD 12 HS	Premotor cortex	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, > 90 V/m) Neuronavigation	Natural frequency	(1) ↓ Main frequency in patients with BPD, MDD and SCZ (11–27 Hz) in comparison with HS (beta-gamma: 21–50 Hz)
Radhu et al. (2015)	38 SCZ 27 OCD 46 HS	Left M1 Left prefrontal cortex	64 channels Sampling rate: 20 kHz	Paired-pulse (monophasic, 1 mV) LICI (ISI: 100 ms) Neuronavigation	Cortical inhibition (ERSP)	(1) ↓ overall DLPFC-LICI inhibition (1–50 Hz) in SCZ vs HS and OCD (2) ↓ DLPFC-LICI in SCZ vs HS in the delta, theta, alpha, beta and gamma bands (3) ↓ DLPFC-LICI in SCZ vs OCD in the theta, alpha and beta bands (4) No differences in M1
Ferrarelli et al. 2015	20 SCZ 20 HS	Parietal cortex Motor cortex Premotor cortex Prefrontal cortex	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120 V/m) Neuronavigation	Source modelling (SCD) Connectivity (SCS)	1) ↓ in SCD and SCS in SCZ patients compared to HS in prefrontal and premotor regions 2) SCD associated with performance in executive functions, SCS associated with performance in episodic memory 3) No between-group difference for motor and parietal regions
Radhu et al. (2017)	19 SCZ or SAD 30 first-degree relatives of SCZ 13 OCD 18 first-degree relatives of OCD 49 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single/paired pulse (monophasic, 1 mV) LICI (ISI: 100 ms) Neuronavigation	Cortical inhibition, oscillations (ERSP)	(1) ↓ frontal LICI and gamma inhibition in SCZ only (2) 89% sensitivity of gamma inhibition to classify SCZ patients
Noda et al. (2017a)	12 SCZ 12 HS	Left M1 Left DLPFC	64 channels Sampling rate: 20 kHz	Single pulse (monophasic, 1 mV) SAI (ISI: N20 + 2 M1, N20 + 4 DLPFC) Neuronavigation	TEPs (SAI inhibition)	(1) M1: more pronounced P180 increase in SCZ vs HS (2) DLPFC: ↓N100 in SCZ vs ↑N100 in HS

Legend: BPD: bipolar disorder; DLPFC: dorsolateral prefrontal cortex; ERSP: event-related spectral perturbation; ITC: intertrial coherence; ISI: interstimulus interval; GMFP: global mean field power; HS: healthy subjects; LICI: long-interval intracortical inhibition; MDD: major depression disorder; MSO: maximal stimulator output; OCD: obsessive-compulsive disorder; RMT: resting motor threshold; SAI: short latency afferent inhibition; SAD: schizoaffective disorder; SCD: significant current density; SCS: significant current scattering; SCZ: schizophrenia; TEP: TMS-evoked potential.

SCZ, a mechanism which is thought to be involved in the pathophysiology of the disorder. Following a study conducted in healthy subjects showing that the electrophysiological marker of LICI in DLPFC is a selective reduction of gamma oscillations (Farzan et al., 2009), Farzan et al. (2010a) aimed at examining this EEG measure of LICI in SCZ patients, in comparison with healthy con-

Table 5
Mood disorders.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Neurophysiology						
Canali et al. (2015)	12 MDD 12 BPD 12 SCZ 12 HS	Premotor cortex	60 channels Sampling rate: 1450 Hz	Single pulse (>90 V/m) Neuronavigation	Natural frequency	(1) ↓ Main frequency in patients with BPD, MDD and SCZ (11–27 Hz) in comparison with HS (beta-gamma: 21–50 Hz)
Intervention						
Casarotto et al. (2013)	8 TRD	Left or right superior frontal gyrus	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90–130 V/m) Neuronavigation	TEPs (IRA, IRS) Pre and post ECT: twice a week with bilateral electrode placement (from 3 to 9 sessions)	(1) ↑ IRA in frontal regions after ECT in all patients (2) ↑ IRS of early TEPs after ECT (5 patients)
Canali et al. (2014)	21 MDD with BPD type I	Bilateral PFC	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90–130 V/m) Neuronavigation	TEPs (IRA, IRS, GMFP) Cortical oscillations Pre and during one week of chronotherapy (6 time-points including morning, evening, sleep, sleep deprivation)	(1) ↑ TEPs slope values during treatment (2) ↑ baseline cortical excitability (GMFP and IRA) in responders than non-responders (3) Responders showed lower increase in EEG theta power after sleep deprivation
Sun et al. (2016)	27 TRD	Left DLPFC Left M1	64 channels Sampling rate: 20 kHz	Single/paired-pulse (monophasic, 1 mV) LICI (ISI: 100 ms) Neuronavigation	Cortical inhibition 1 week before MST: 24 sessions or until remission	(1) N100 and LICI in frontal cortex were indicators of remission of suicide ideation (2) No correlation with motor cortex N100 and LICI
Pellicciari et al. (2017a)	1 TRD	Bilateral DLPFC	62 channels Sampling rate: NA	Single pulse (90% RMT) Neuronavigation	Prefrontal oscillatory activity Pre/Post: 10 sessions of left iTBS/ right cTBS	(1) Pre-treatment: asymmetry of DLPFC cortical activity (left alpha, right beta and gamma) (2) Post-treatment: left ↓ theta and alpha, ↑ beta/gamma; right ↑ alpha
Canali et al. 2017	18 MDD with BPD 9 HS	Superior frontal gyrus (BA6)	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90–130 V/m) Neuronavigation	Premotor dominant frequency Pre and post one week of chronotherapy	(1) ↓ frontal frequencies (19 Hz) than HS (27 Hz; beta/gamma band) (2) No significant change in main frequency pre/post treatment, and between responders and non-responders
Noda et al. 2018	29 MDD 28 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single pulse (biphasic, 1mV)	Cortical oscillations Pre and post 1 session of PAS25 applied to left DLPFC	(1) PAS induced ↑ power in delta, theta and gamma bands in HS vs MDD; and ↑ theta-gamma coupling in HS vs MDD

Legend: BA: Brodmann area; BDP: bipolar disorder; cTBS: continuous theta burst stimulation; DLPFC: dorsolateral prefrontal cortex; ECT: electroconvulsive therapy; IRA: immediate response area; IRS: immediate response slope; ISI: interstimulus interval; iTBS: intermittent theta bust stimulation; HS: healthy subjects; LICI: long-interval intracortical inhibition; M1: primary motor cortex; MDD: major depression disorder; PAS: paired-associative stimulation; NA: not available; RMT: resting motor threshold; TEP: TMS-evoked potential; TRD: treatment resistant depression.

Table 6
Substance use disorders.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Naim-Feil et al. (2016)	12 ALD post-detoxification 14 HS	Bilateral DLPFC	24 channels Sampling rate: 20 kHz	Single/paired pulse (biphasic, 1 mV) LICI (ISI: 100 ms)	Cortical inhibition (50–150 ms)	(1) ↓ LICI in both DLPFC in ALD patients relative to HS (2) No difference in single pulse area under curve

Legend: ALD: alcohol dependent; DLPFC: dorsolateral prefrontal cortex; ISI: interstimulus interval; HS: healthy subjects.

Table 7
Autism spectrum disorders.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Jarczok et al. (2016)	21 ASD 22 HS	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (1 mV)	Connectivity	(1) No difference between interhemispheric signal propagation between both groups
Kirkovski et al. (2016)	22 ASD 20 HS	Right DLPFC Right M1 Right temporo-parietal junction	20 channels Sampling rate: 10 kHz	Single pulse (monophasic, 1 mV)	Power Phase and power synchrony	(1) No difference in power and phase synchrony between groups across all frequencies and sites (2) Higher level of autistic traits were related to less phase synchrony in the M1 beta band

Legend: ASD: autism spectrum disorder; DLPFC: dorsolateral prefrontal cortex; HS: healthy subjects; M1: primary motor cortex.

Table 8
Attention deficit hyperactivity disorder.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Behavioural tasks						
Bruckmann et al. (2012)	20 ADHD children 19 HS age-matched	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 105% RMT)	N100 component At rest and during movement execution and reaction time task	(1) ↓ N100 in ADHD (2) Tendency for ↓ latency of N100 in ADHD (3) No reduction of N100 during movement preparation in ADHD, less reduction of the N100 during movement execution
D'Agati et al. (2014)	18 ADHD children 19 HS age-matched	Left M1	22 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 1 mV)	N100 component At rest and during a go/nogo task	(1) No difference in amplitude of the N100 at rest in ADHD (2) Smaller N100 modulation during a go/nogo task
Intervention						
Helfrich et al. (2012)	25 ADHD children	Left M1	64 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 110% RMT)	N100 amplitude Pre, during and post 1 Hz rTMS vs sham rTMS	(1) ↓ N100 during (0–500 pulses) and after rTMS, while no difference in sham group

Legend: ADHD: attention deficit hyperactivity disorder; HS: healthy subjects; M1: primary motor cortex; RMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation.

trols and patients with bipolar disorder. SCZ patients displayed impaired inhibition of gamma oscillations induced by LICI (DLPFC target), while normal gamma oscillatory activity was obtained in response to single-pulse TMS over the same area. This suggests that inhibitory control rather than the generation of gamma oscillations may be specific to the pathophysiology of SCZ and could become a neurophysiological marker of frontal inhibitory deficits in the disorder (Farzan et al. 2010a). The same research group subsequently investigated the specificity of LICI deficits in motor and prefrontal areas in SCZ patients as well as in individuals with obsessive-compulsive disorder (OCD) (Radhu et al., 2015). SCZ patients showed reduced inhibition of gamma oscillations induced by LICI in comparison with controls and in individuals with OCD in the prefrontal cortex, but not in M1. This study hence provided further support for frontal-cortex GABAergic deficits in SCZ. More recently, the integrity of prefrontal LICI was investigated in SCZ and their first-degree unaffected relatives (Radhu et al., 2017). Reductions in LICI and gamma inhibition were observed only in the DLPFC of SCZ patients but not in first-degree unaffected relatives, suggesting that these deficits are specific to the pathophysiology of the disorder and could become a potential target for therapy or objective marker of the disorder. In addition, prefrontal cholinergic cortical inhibition was recently assessed using the novel prefrontal SAI protocol (see Section 5.3 (Noda et al., 2015a)) in SCZ patients (Noda et al., 2017a). Altered modulation of the N100 component following SAI was found, whereas SCZ patients displayed a decrease rather than an increase of the amplitude of the component. This suggests that frontal cholinergic circuits may also be altered in SCZ as assessed with TMS–EEG.

TMS-induced natural frequencies in motor and frontal regions: From TMS-EEG studies in healthy controls on the oscillatory response profiles of different areas to single pules TMS, it was inferred that different cortical regions are associated with specific natural frequencies reflecting local intrinsic properties of the stimulated networks (Rosanova et al., 2009). In keeping with this, Ferrarelli et al. (Ferrarelli et al., 2008) aimed at evaluating the integrity of natural premotor frequencies, namely, gamma oscillations, induced by TMS in SCZ patients. In comparison with controls, SCZ patients displayed altered amplitude, synchronization and propagation of gamma oscillations, suggestive of impairments in fronto-thalamo-cortical circuits responsible for producing and synchronizing gamma oscillations (Ferrarelli et al., 2008). In a follow-up study, natural frequencies were investigated in namely parietal, motor, premotor and prefrontal areas, and compared between SCZ patients and controls (Ferrarelli et al., 2012). A specific reduction in TMS-related amplitude and synchronization of beta/gamma oscillations in frontal/prefrontal areas was found, as well as a slowing of prefrontal natural frequency in SCZ patients. This altered prefrontal frequency was related to positive symptom severity and reaction time in a verbal memory task. The authors concluded that impaired generation of high frequencies in frontal regions may be related to decreased GABAergic control on excitatory neurons (Ferrarelli et al., 2012). Canali and collaborators (Canali et al., 2015) further assessed the integrity of frontal oscillatory properties across several psychiatric disorders, including SCZ. In line with the previous studies, TMS of the premotor cortex was shown to be associated with gamma/beta-band responses in healthy controls, while SCZ patients displayed a main frequency in a lower band (11–27 Hz).

Excitability and connectivity studies: Given the heterogeneity of deficits which characterize SCZ, Frantseva et al. (2014) suggested that a failure to integrate the activity of local and distributed neural circuits, presumably related to inhibitory interneuron dysfunctions, may partially underlie the complex symptomatology of the disorder. To test this hypothesis, the authors checked for disrupted patterns of TMS-evoked cortical signal propagation in SCZ patients using TMS–EEG applied to M1. The results revealed that the initial response to TMS was of similar amplitude in patients and controls. However, patients displayed excessive spread of neural excitation: while controls showed a response limited to the stimulated site that lasted up to 300 ms, patients showed widespread and delayed activity around 200 ms and between 400 and 750 ms. Patients also displayed increased oscillatory activity in the gamma, beta and delta bands at 400–700 ms, suggesting that the initial local decrease in natural frequency observed in previous studies (Ferrarelli et al., 2008, 2012; Canali et al., 2015) may be followed by excessive aberrant cortical activations in adjacent and remote areas. Of note, positive and negative symptoms were correlated with some aspects of cortical signal propagation, indicative of a possible functional impact of these abnormalities.

Study of task-related activity using TMS-EEG: Ferrarelli and colleagues (Ferrarelli et al., 2015) aimed at assessing measures of parietal, motor, premotor and prefrontal cortical activity (SCD) and connectivity (SCS), and explore for potential relationships with impaired episodic memory and executive function. Patients with SCZ showed reduced activity in the anterior frontal areas (prefrontal and premotor) following TMS, as revealed by reduced source density in those regions compared to controls, while

responses in parietal and motor cortices were intact. Connectivity in frontal regions was also found to be reduced in patients. Functional relationships were found between the degree of activity in frontal areas and memory performance, as well as between connectivity in frontal areas and scores in executive-function tasks. These findings point towards altered effective communication between frontal regions and other cortical areas, consistent with previous TMS–EMG and TMS–fMRI work (Rogasch et al., 2014).

6.1.1.1. Summary and future clinical applications: Schizophrenia. TMS–EEG has been used extensively to better understand the neurophysiological characteristics of SCZ. As described above, those studies helped to corroborate and extend the results derived from other techniques such as TMS–EMG, providing further evidence for altered cortical inhibition (e.g., LICI) and novel evidence on the electrophysiological markers (e.g., abnormal generation and modulation of gamma oscillations, connectivity) in frontal regions. These converging findings emphasize the promise of translating results into clinical applications, such as development of novel neurophysiological and cortical targets for therapeutic interventions (Rogasch et al., 2014). As such, the scope of clinical applications of TMS–EEG in SCZ is very large. The recent development of novel paired-pulse TMS–EEG measures of cortical inhibition/excitation, such as ICF and SICI (Cash et al., 2017), could help a better characterization of inhibitory and excitatory imbalance in SCZ. As previous TMS studies have shown, altered plasticity in SCZ (Hasan et al., 2013) and GABAergic inhibition are strongly involved in cortical plasticity mechanisms. Future studies could employ TMS–EEG to study the integrity of cortical plasticity in non-motor regions using techniques such as TBS and the novel PAS protocol for DLPFC (see Section 5.2; (Rajji et al., 2013)). Moreover, TMS–EEG remains to be used to study the effects of several therapeutic interventions on neural circuits in SCZ, such as deep brain stimulation (DBS), rTMS and pharmacology (Kaskie and Ferrarelli, 2018). Importantly, longitudinal TMS–EEG studies conducted among large groups including several stages of the illness and different predominant symptoms (e.g., positive vs. negative) are necessary to better understand the neurophysiological processes underpinning this severe mental health disorder.

6.1.2. Mood disorders

Major depressive disorder (MDD) is the most common mood disorder. It is characterized by the presence of depressed mood and/or loss of interest, as well as a number of somatic, vegetative and psychological symptoms (Doris et al., 1999). Although the therapeutic armamentarium available for treating MDD has expanded substantially over the last decades, treatment-resistant/refractory major depression (TRD), in its broadest sense, still characterizes a significant number of patients (Fava and Davidson, 1996; Berlim and Turecki, 2007). Indeed, about one third of patients treated for MDD do not respond satisfactorily to initial antidepressant pharmacotherapy (Berman et al., 1997). Furthermore, a considerable proportion of cases have a poor prognosis, with as much as 20% still being ill 2 years after the onset of illness (Keller, 2005; Souery et al., 2006). The most effective treatment for patients with TRD is still electroconvulsive therapy (ECT) (Bewernick and Schlaepfer, 2015). However, the mechanisms underlying the antidepressant effect of ECT remain elusive and adverse effects remain present despite improvements in methods. This has stimulated the development of alternative treatments in the past few decades.

The neurobiology of MDD is complex. TMS–EMG studies have previously suggested altered patterns of cortical inhibition/excitation in the motor cortex (e.g., reduced SICI) as part of the pathophysiology of the disorder (Bunse et al., 2014). Using resting EEG, converging lines of evidence suggest altered oscillatory patterns in MDD (Fingelkurts and Fingelkurts, 2015). For example, studies have shown frontal interhemispheric asymmetry, i.e., reduced left and increased right frontal activity (Funk and George, 2008). This stimulated the development of rTMS treatments of frontal areas to restore this asymmetry. rTMS is approved by the US FDA since 2008 and is now a first-line evidenced-based accepted treatment after failure from one antidepressant therapy (Kennedy et al., 2009; Lefaucheur et al., 2014). While resting EEG (e.g., (Kazemi et al., 2016; Noda et al., 2017c)) and neuroimaging methods (e.g., (Bai et al., 2016; Kang et al., 2016)) have been widely used to assess the effect of rTMS, TMS–EEG provides a highly sensitive alternative, which has only very recently gained interest in the field. The majority of studies employed TMS–EEG as a marker of the effect of different types of interventions, namely ECT, magnetic seizure therapy, PAS and theta-burst stimulation, while only one TMS-EEG study investigated neurophysiological aspects of the disorder. The main results are shown in Table 5 and will be discussed below.

As stated above, ECT is often used for treating TRD. However, little is known about its underlying effect on brain activity. A group of researchers investigated the effect of a course of ECT treatment on the frontal cortex in patients with TRD (Casarotto et al., 2013) and showed increased cortical excitability amplitude (as measured by IRA and IRS) in frontal areas following ECT. A trend for a positive relationship between increased early TEP spectral power and mood improvements was also reported. These neurophysiological changes may be reflecting cortical plasticity mechanisms resulting from the treatment and show the utility of TMS–EEG in measuring objective neurophysiological changes induced by ECT. Magnetic seizure therapy (MST) has recently been developed as an alternative to ECT, which is associated with less cognitive adverse effects (Engel and Kayser, 2016). Using TMS–EEG, Sun et al. (2016) assessed if baseline cortical inhibition in TRD can predict the effect of a treatment course of MST on suicidal ideations. A greater decrease in the suicidal ideations was associated with a more negative N100 value and a greater baseline LICI value. This suggests that greatest cortical inhibition at baseline is an indicator of remission of suicide ideations. Together, both values could predict resolution of suicidal ideation with high specificity and sensitivity (89% accuracy, 90% sensitivity, 89% specificity). This study highlights how baseline neurophysiological measures, such as levels of cortical inhibition, could eventually help in selecting patients that are more likely to respond to a specific treatment. In line with results from both studies, it would be highly interesting to compare changes induced by MST and ECT on frontal excitability and inhibition.

As discussed in Section 5.3, TBS is a relatively novel rTMS protocol, which requires significantly lower stimulation duration and intensity than conventional rTMS. Because of those two major advantages, recent trials investigated its effect in MDD and showed similar effects as those obtained with rTMS (Chung et al., 2016). A recent case study assessed the effect of 10 sessions of bilateral DLPFC theta-burst stimulation (left iTBS and right cTBS) on frontal oscillatory frequencies (Pellicciari et al., 2017a). The results highlighted a strong asymmetry of DLPFC cortical oscillatory activity at baseline, with left alpha-band oscillations and right beta/gamma frequencies. Bilateral TBS induced a rearrangement of oscillatory activity of both DLPFCs paralleled by clinical improvement, via the modulation of both slow and fast prefrontal cortical oscillatory activity. Furthermore, the impact of a single session of DLPFC-PAS on prefrontal cortical oscillations in MDD was recently studied (Noda et al. 2018). Healthy controls showed increased power in delta, theta and gamma bands, and increased theta-gamma coupling following PAS, whereas no effect was obtained in MDD individuals. These results point towards altered prefrontal plasticity in MDD.

As presented in Section 6.1.1, Canali et al. (2015) showed a shared lower main natural frequency of frontal regions in SCZ, MDD, as well as another major mood disorder, i.e., bipolar disorder (BP), in comparison with healthy individuals. This is likely the result of a shared neurobiological mechanism of corticothalamic impairment in those psychiatric disorders (Canali et al., 2015).

As just stated, BP is a common mood disorder that is thought to share some neurophysiological features with MDD. BP is characterized by a pattern of full remission of manic and depressive disorders, with type I referring to the occurrence of at least one lifetime manic episode and type II referring to the presence of hypomanic and depressive episodes (Manji and Zarate, 2011). Similar neuromodulation treatments to those used in MDD have been employed to alleviate of depression in BP. For instance, a few trials have shown promising effects of rTMS for treating depressive phases in BP and modifying frontal electrophysiological activity (Kazemi et al., 2016). In a series of studies, the effect of a novel family of treatments, i.e., chronotherapeutics (combined sleep deprivation and light therapy), have been assessed in MDD patients with a type I BP using TMS–EEG (Canali et al., 2014, 2017) (see Table5). TMS–EEG measures were acquired at baseline as well as at six different time points during treatment; changes in the slope of TEPs over the course of the treatment were observed, which might indicate that altered cortical excitability prompted by sleep deprivation could be related to shifts in synaptic efficiency and neuroplasticity (Canali et al., 2014). Data from this study were further analyzed to investigate the effect of chronotherapy on the dominant frequencies induced by premotor TMS (Canali et al., 2017). MDD patients with type I BP displayed lower gamma/beta frequency at baseline, compared to a group of healthy controls. Evoked brain oscillations did not change following treatment, remaining lower than controls, and this was independent of achieving remission. The authors suggest that a reduction of natural frontal frequencies may represent a trait of MDD with BP as previously shown (Canali et al., 2015).

6.1.2.1. Summary and future applications: Mood disorders. Findings from these studies support the use of TMS–EEG in mood disorders to better understand the effect of different antidepressant therapies on neural function and possibly help identify patients who are likely to respond to a specific type of treatment. Because neuromodulation methods, such as ECT, MST and rTMS, are frequently used in clinical settings among this population, the clinical application of TMS–EEG is highly significant and could eventually become a central part of the clinical armamentarium. Future studies should focus on comparing the effect of different neuromodulation treatments on all indexes of TMS-evoked activity, as well as investigating the effect of pharmacotherapy and psychotherapy. TMS–EEG also provides unique insight into the pathophysiology of depression, which remains to be further explored.

6.1.3. Substance use disorders

Substance use disorders (SUDs) are chronic relapsing brain disorders associated with important economic and healthcare burden, for which effectiveness of therapies and understanding of the underlying pathophysiology remain limited (Yavari et al., 2016). Alcohol dependence is a common type of SUDs, with a US prevalence rates of 7.4% and 4.7% for men and women, respectively (Azevedo and Mammis, 2018). Among several other neurotransmitters, alcohol is known to have an effect on GABAergic and glutamatergic transmission (Morikawa and Morrisett, 2010; Ravan et al., 2014). There is a recent interest in using TMS as a mechanistic and therapeutic tool in alcohol addiction (Yavari et al., 2016). For instance, TMS–EMG studies over M1 have shown cortical inhibition and excitation impairments, such as increased cortical silent period and increased motor thresholds (see (Yavari et al., 2016) for review).

Despite the great potential of TMS–EEG in the study of SUDs, to our knowledge, only one study used the technique to study alcohol dependence (Table 6). Naim-Feil and colleagues (Naim-Feil et al. 2016) specifically investigated cortical inhibition in alcohol-dependent (ALD) patients post-detoxification. Patients displayed reduced cortical inhibition (LICI) in both DLPFCs that could reflect reduced GABAergic activity within the prefrontal components of the mesocorticolimbic circuitry. In addition, the acute effect of ethanol consumption in healthy controls was also studied using TMS–EEG in a series of studies conducted by Kähkönen and colleagues (for review: (Kähkönen, 2006)) where alcohol was found to induce reductions in prefrontal cortical excitability, as assessed by TEP amplitude and GMFA ((Kähkönen et al., 2001, 2003), reductions in the TMS-evoked N100 response on motor cortex (Kähkönen and Wilenius, 2007), and changes in functional connectivity between motor and prefrontal cortices (Kähkönen et al., 2001).

6.1.3.1. Summary and future clinical applications: Substance use disorders. TMS–EEG could undeniably contribute to current knowledge on neural and network alterations in SUD. As both invasive and non-invasive brain stimulation techniques have been shown as promising clinical tools for treatment of SUD (Spagnolo and Goldman, 2016; Yavari et al., 2016), focus should be put on using TMS–EEG to better understand the neural correlates of the effect of those techniques in patients. Measures of TMS-evoked activity, such as TEPs and evoked oscillations, could also be employed for exploring potentials for pharmacological interventions, monitoring brain plasticity over time, treatment individualization and outcome prediction (Yavari et al., 2016). Importantly, future studies should also focus on other important SUDs, such as cannabis and nicotine addiction.

6.1.4. Autism spectrum disorder

Autism spectrum disorder (ASD) is a neuropsychiatric developmental disorder characterized by symptoms in two core domains, i.e., social-communication deficits and repetitive behaviors and restricted interests. Although the etiology of ASD remains poorly understood, recent studies propose that an excitatory–inhibitory imbalance in neural circuits (Uzunova et al., 2015), as well as disrupted structural and functional connectivity (Mohammad-Rezazadeh et al., 2016) may play important roles in the pathophysiology of the disorder. Two studies have recently applied TMS–EEG in a population of ASD (Table 7).

Based on evidence showing structural alterations in the corpus callosum (CC) in ASD, Jarcok and colleagues (Jarczok et al., 2016) assessed differences in inter-hemispheric cortico-cortical connectivity in childhood and adolescence in ASD individuals compared to typically developing controls. The index of connectivity (inter-hemispheric signal propagation, ISP) correlated with age, and therefore with the maturation of the corpus callosum in both groups. However, contrary to the hypothesis of reduced connectivity in ASD, no deficit was found in interhemispheric signal transfer between the primary motor cortices. The authors suggest that although small structural alterations have previously been shown in the CC, other structures that are more closely related to the pathophysiology of ASD core deficits (e.g., DLPFC) may be more reliable targets for investigations TMS–EEG investigation of the integrity of connectivity in the neurodevelopmental disorder.

In keeping with the excitatory/inhibitory imbalance theory, another study primarily aimed at assessing the power and connectivity in EEG high-frequency bands (i.e., gamma and beta) related to the GABA system in three different sites thought to be involved in ASD: DLPFC, M1 and right temporoparietal junction (Kirkovski et al., 2016). No significant differences were found between a

group of ASD adults and matched healthy volunteers in oscillatory activity (power and phase) and connectivity (power synchrony) in all frequency bands across all cortical sites. However, some non-significant trends were reported, suggesting reduced beta-band phase synchrony in ASD, which correlated with higher levels of autistic traits. The authors suggest that sample selection, which mainly included high functioning adults with ASD, may have influenced the results. Nevertheless, they propose that subtle neurophysiological differences in cortical reactivity may be related to specific traits or characteristics of adults with ASD.

6.1.4.1. Summary and future clinical applications: Autism spectrum disorder. As of now, two TMS–EEG studies in ASD have both reported negative results. However, both studies were preliminary in nature, with limitations in the population samples tested (study 1, high heterogeneity; study 2, high-functioning ASD adults). Nevertheless, several TMS–EMG studies have recently explored for the development of potential physiological biomarkers of ASD, such as impaired cortical inhibition, and of potential for rTMS as a therapeutic intervention (Oberman et al., 2016). In this context, TMS–EEG, as a measure of cortical inhibition and connectivity, represents a valuable research tool that should be further employed.

6.1.5. Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neuropsychiatric disorder in childhood; it is mainly characterized by impulsivity, hyperactivity and inattention. Impaired cortical inhibitory function is thought to play a major role in the pathophysiology of ADHD, related to inefficient top-down regulation of the frontal-subcortical executive control system (Martinez et al., 2016). In addition, impaired motor cortical inhibition (i.e., SICI) has been highlighted by TMS studies over the motor cortex; this impairment was shown to be related to motor hyperactivity (Dutra et al., 2016). TMS–EEG studies conducted among this population have focused on measuring cortical inhibition during a behavioral task involving inhibition, as well as in conjunction with plasticity-inducing non-invasive protocols (see Table 8).

TMS–EEG was first used to assess to what extend top-down control contributes to reduced motor-cortex inhibition in ADHD: TMS-evoked N100 at rest and during movement preparation and execution was examined (Bruckmann et al., 2012). ADHD children displayed reduced N100 amplitude and a tendency for reduced N100 latency at rest, providing further evidence for a motor inhibitory deficit. In typically developing children, movement execution was associated with a strong decrease in N100 amplitude and increase in MEP amplitude, supporting the idea that both measures provide independent information. The decrease in N100 amplitude was observed to a lesser degree in ADHD, suggesting a reduced capacity for altering inhibition during movement execution.

Similarly, D'Agati and colleagues investigated the TMS-evoked N100 at different processing stages of a response control (Go NoGo) task in ADHD children (D'Agati et al., 2014). Contrary to the previous study, ADHD children did not display abnormal N100 amplitudes during response preparation and at rest. However, reduced modulation of the N100 during movement execution and inhibition (go and no-go trials) was observed, supporting findings from Bruckmann et al. (2012).

TMS–EEG was also used to monitor real-time effects of rTMS in children with ADHD, showing that the N100 amplitude is first reduced and then reaches a plateau during 1-Hz rTMS applied to M1 (Helfrich et al., 2012). The study also showed reduced N100 amplitude after 1-Hz rTMS compared to sham rTMS. This points toward a potential clinical use of rTMS to modulate abnormal cortical inhibition in ADHD children. Interestingly, the N100 was shown to be more sensitive to induced changes than MEPs, which were not significantly modulated by 1-Hz rTMS.

6.1.5.1. Summary and future clinical applications: Attention deficit hyperactivity disorder. Two studies support the idea that the N100 can be a marker of abnormal motor-cortical inhibition in ADHD. In addition, they both suggest that the TMS-evoked N100 can provide additional information than MEPs. The study by Helfrich et al. (Helfrich et al., 2012) also contributed to establishing TEPs as a useful approach for monitoring cortical excitability changes during plasticity-inducing protocols, and may therefore contribute to the safety of rTMS in populations for which studies are lacking such as children. Future studies should focus on other cortical regions such as the DLPFC and during cognitive inhibition task. In line with impaired SICI over M1, the use of paired-pulse paradigm with TMS–EEG could also help shed light into the presence of inhibitory deficits in frontal regions such as the DLPFC.

6.2. Neurology

Neurological disorders encompass a large collection of disorders affecting the central nervous system, from acquired brain injury such as stroke to neurodegenerative diseases. Since its introduction in 1985 (Barker et al., 1985), TMS–EMG has greatly contributed to our knowledge of the neurobiology of several neurological disorders, especially of those primarily affecting the motor system, such as movement disorders, but also of conditions arising from non-motor regions (Curra et al., 2002; Chen et al., 2008). Moreover, the use of NTBS protocols, such as tDCS and rTMS as potential treatments has been increasingly explored (Lefaucheur et al., 2014, 2017). Until now, TMS–EEG has been employed in five different neurological disorders, namely Alzheimer's disease, stroke, Parkinson's disease, Huntington's disease, disorders of consciousness, mild traumatic brain injury and epilepsy. The main results are shown in Tables 9–14. A summary of findings and clinical prospective for each disorder will be presented in the current section.

6.2.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia. It is characterized by progressive neuronal degeneration associated with neurofibrillary tangles and the formation of beta-amyloid plaques, first affecting medial temporal lobe structures and then progressing through limbic structures and cortical areas. Mild cognitive impairment (MCI) is considered a prodromal stage of AD, as it is associated with increased risk of developing AD. Tools are currently lacking to help diagnose AD in the early stages of the disease, before structural changes can be observed. Resting EEG and neuroimaging have contributed to a better understanding of AD and MCI, suggesting altered connectivity that may occur prior to the onset of structural changes (Dipasquale and Cercignani, 2016; Teipel et al., 2016). TMS–EMG studies have also contributed to the understanding of neurophysiological biomarkers of AD, with evidence suggesting hyperexcitability of M1 in the early stages of the disease, as well as altered cortical inhibition (SICI) and cholinergic short-latency afferent inhibition (SAI) (Cantone et al., 2014; Ni and Chen, 2015). Four studies have assessed the use of TMS–EEG as a measure of neurophysiology of AD, while two studies measured neural changes induced by NTBS interventions using TMS–EEG (see Table 9).

Julkunen and colleagues (Julkunen et al., 2008a) were the first to employ TMS–EEG in a small sample of AD and MCI patients (5 patients per group). They compared connectivity and cortical reactivity of both groups with controls. AD patients showed depressed TMS-evoked responses at around 30–50 ms over large areas corresponding to the sensorimotor network, which the authors linked to decreased cortical reactivity and connectivity, or a lack of synchronization of cortical responses. MCI patients displayed a P30 amplitude ranging between the value of AD patients and healthy subjects, suggesting that TMS–EEG is sensitive to this transitional

Table 9
Alzheimer's disease.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Neurophysiology						
Julkunen et al. (2008)	5 AD 5 MCI 4 HS	Bilateral M1	60 channels Sampling rate: 1024 Hz	Single pulse (monophasic, 110% RMT) Neuronavigation	TEPs (time, frequency, space)	(1) AD: ↓ P30 in ipsilateral temporo-parietal and contralateral fronto-central regions in comparison with HS (2) MCI: ↑ P30 amplitude in comparison with AD
Julkunen et al. (2011)	5 AD 5 MCI 4 HS	Bilateral M1	60 channels Sampling rate: 1024 Hz	Single pulse (monophasic, 110% RMT) Neuronavigation	TEPs (time, frequency, space) Clinical dementia rating scale	(1) ↑ P30 amplitude in sensorimotor system in AD (2) P30 amplitude can discriminate between AD and HS (75% sensitivity, 80% specificity), and between AD and MCI (80% sensitivity and 78% specificity)
Casarotto et al. (2011)	9 young HS 9 elderly HS 9 AD	Left superior frontal cortex	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 100–120 V/m) Neuronavigation	TEPs (time, SCD)	(1) SCD ↔ between young and elderly HS (2) SCD is ↓ in AD compared to both young and elderly HS
Ferreri et al. (2016)	12 AD 12 HS	Left M1	32 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 120% RMT) Neuronavigation	TEPs (time, frequency, space) Clinical dementia rating scale	(1) ↑ P30 in sensorimotor system and ↑ activity at 60–80 ms in somatosensory cortices in AD
Intervention						
Kumar et al. (2017)	32 AD 16 HS	Left DLPFC	64 channels Sampling rate: 20 kHz	Single pulse (monophasic, 1 mV) Neuronavigation	TEPs-mean evoked cortical activity Pre and 0, 17, 34 min post DLPFC PAS25	(1) AD showed reduced potentiation of cortical-evoked activity (post/pre) in comparison with HS (2) Positive correlation between potentiation of cortical-evoked activity and working memory performance (n-back task) in both groups
Koch et al. (2018)	14 AD	Precuneus Left posterior parietal cortex (control site)	29 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 90% AdjRMT) Neuronavigation	TEPs GMFP Cortical evoked oscillations Connectivity (ITC) 2-week sham-controlled crossover 20-Hz rTMS treatment over precuneus	(1) ↑ P3 post rTMS treatment in the precuneus (2) ↑ GMFP amplitude 60–90 ms post treatment in frontal, and parieto-occipital regions (3) ↑ beta power and ITC over parietal regions post treatment

Legend: AD: Alzheimer's disease; HS: healthy subjects; M1: primary motor cortex; RMT: resting motor threshold; TEP: TMS-evoked potential; SCD: significant current density.

Table 10
Stroke.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Intervention						
Cipollari et al. (2015)	6 non-fluent aphasia	Right inferior frontal gyrus	20 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 90% RMT) Neuronavigation	TEPs Pre and post anodal and sham tDCS combined with language treatment (15 sessions)	(1) language treatment and anodal tDCS + treatment: ↑ amplitude of TEPs at 87 ms (2) Anodal tDCS + treatment: ↑ amplitude of TEPs at 118 ms
Neurophysiology						
Manganotti et al. (2015)	9 acute stroke 7 HS	Left M1	32 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 110% RMT) Neuronavigation	TEPs	(1) Favorable outcome was associated with reliable N100 TEP responses (2) Presence of N100 TEP in the absence of MEP was a predictor of outcome
Borich et al. (2016)	10 chronic stroke 4 HS	Bilateral M1	64 channels Sampling rate: 2000 Hz	Single pulse (monophasic, 1 mV) Neuronavigation	Interhemispheric connectivity in beta frequency range	(1) ↑ beta coherence between both M1 during ipsilateral contraction in stroke (2) No difference at rest
Pellicciari et al. (2018)	13 sub-acute subcortical stroke 10 HS	Bilateral M1 Bilateral parietal cortex	29 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 90% RMT) Neuronavigation	TEPs GMFP EOR 20 (t0-baseline), 40 (t1), 60 (t2), and 180 (t3) days post-stroke	(1) Baseline M1 (vs. controls): bilateral ↓ GMFP and TEP amplitudes; bilateral ↓ alpha and beta EOR; ↓ delta EOR in UH (2) Longitudinal M1: ↑ GMFP (t1-t2) and alpha activity (t1-t2-t3) in AH (vs. UH) (3) Significant positive correlation between alpha EOR and clinical scores at all time points

Legends: AH: affected hemisphere; EOR: evoked-oscillatory response; GMFP: global mean field power; HS: healthy subjects; M1: primary motor cortex; RMT: resting motor threshold; TEP: TMS-evoked potential; UH: unaffected hemisphere.

Table 11
Parkinson's disease.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/Intervention	Main result(s)
Intervention						
Casula et al. (2017)	6 PD 8 HS	Left M1	19 channels Sampling rate: 5000 Hz	Single pulse (monophasic, 90% RMT) Neuronavigation	TEPs Spectral power During: 1) LD + STN-DBS, 2) STN-DBS, and 3) STN-DBS off	(1) All components showed ↑ amplitude in HS in comparison with the three PD conditions (2) STN-DBS ↑ 45–80 ms TEPs and ↑ alpha-oscillations 3) LD therapy ↑80-130 ms TEPs and ↑beta oscillations

Legend: HS: healthy subjects; LD: levodopa; M1: primary motor cortex; PD: Parkinson's disease; STN-DBS: subthalamic nucleus deep brain stimulation; RMT: resting motor threshold; TEP: TMS-evoked potential.

Table 12
Huntington's disease.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Casula et al. (2018)	16 preHD mutation carriers 16 HS	Left M1 Left PM	32 channels Sampling rate: 2048 Hz	Single pulse (monophasic, 90% RMT) Neuronavigation	TEPs (GMFP) Cortical evoked oscillations (ERSP, ITC)	(1) preHD – M1: ↑ TEP amplitudes in motor cortex region 150–250 ms post TMS; ↑ P3 (GMFP) (2) preHD – M1: ↓ ITC in the theta band and alpha band 3) Negative correlation between ITI-SD and GMFP-P3 and ITC-theta

Legend: ERSP: event-related spectral perturbation; GMFP: global mean field power; HS: healthy subjects; ITC: intertrial coherence; ITI-SD: intertap interval standard deviation; M1: primary motor cortex; PM: premotor cortex; preHD: presymptomatic Huntington's disease; RMT: resting motor threshold; TEP: TMS-evoked potentia.

Table 13
Mild traumatic brain injury.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Bashir et al. (2012)	1 mTBI 12 HS	Left M1	Info not available	Single pulse (monophasic)	TEPs Week 2 and 6 post mTBI Pre and 0, 5, 10 min post cTBS	(1) Widespread ↑activity at 50 ms at week 2 and 6 (2) cTBS ↑ this activation at week 2 (compared to a decrease in HS), while no change is observed at week 6
Tallus et al. (2013)	11 mTBI (symptomatic) 8 mTBI (asymptomatic) 9 HS	Left M1 Left DLPFC	60 channels Sampling rate: 1450 Hz	Single pulse (monophasic, 90–100-110% of RMT) Neuronavigation	TEPs	(1) DLPFC, symptomatic: delayed ipsilateral P30 and contralateral N45, and ↑ amplitude of N100 (2) DLPFC, asymptomatic: showed ↓ P200 latencies (3) M1, both mTBI groups: less P30 amplitude increase to increasing intensities (4) M1, both mTBI groups: ↑ P60 interhemispheric latency difference with higher stimulation intensities

Legend: cTBS: continuous theta burst stimulation; HS: healthy subjects; mTBI: mild traumatic brain injury; RMT: resting motor threshold; TEP: TMS-evoked potential.

stage. In a subsequent study, Julkunen and colleagues (Julkunen et al., 2011) reanalyzed the previous data in order to investigate subject-specific differences in cortical excitability between MCI, AD patients, and healthy subjects. Specifically, their objective was to assess the ability to discriminate healthy subjects from patients using the P30 amplitude. Results confirmed decreased P30 amplitude in AD and showed that the P30 amplitude could be used to discriminate AD from healthy subjects, as well as AD from MCI. Correlations were found between the P30 and a dementia symptom scale, suggesting a possible relation with cognitive decline. Another TMS–EEG study comparing AD patients with both young and elderly healthy subjects showed that the early and local EEG response to TMS of the left superior frontal cortex is not affected by physiological aging but is significantly impaired in AD (Casarotto et al., 2011).

Another group also studied AD with TMS–EEG in order to further investigate the neurophysiological hallmarks of sensorimotor cortex functionality in AD (Ferreri et al., 2016). Results from this study support the idea of M1 hyperexcitability and extend it to sensorimotor circuits. For instance, compared to healthy controls, the 12 studied AD patients displayed stronger cortical activations (between 60 and 80 ms) that remained segregated to the stimulation area for a longer period which could reflect reverberant local circuits in the sensorimotor system. Hyperexcitability was also observed by an increased P30 amplitude, which is in contrast with results from Julkunen and colleagues. Authors attribute this difference to the fact that the small sample of AD patients in those two previous studies were taking cholinesterase inhibitors which were previously shown to partly recover M1 disinhibition, while the AD patients in the study by Ferreri et al. (2016) were not taking any medication that would interfere with central nervous system excitability.

In a more recent study, Koch et al. (2018) have adopted the TMS–EEG approach to detect neural and connectivity changes induced by a high frequency rTMS treatment applied over the precuneus (PC) of 14 prodromal AD patients, using a sham-controlled crossover design. Findings showed an increase of neural activity in patients' PC, revealed by the enhancement of the power and phase synchronization of brain oscillations in the beta-band, which could suggest modifications of functional connections between the PC

Table 14
Disorders of consciousness.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology						
Rosanova et al. (2012)	5 VS 5 MCS 2 LIS 5 acute coma	Bilateral frontal Bilateral sensory-motor Bilateral parieto-occipital	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 140–200 V/m) Neuronavigation	TEPs Effective connectivity longitudinal measurements during spontaneous clinical evolution	(1) All VS (except one anoxic patient who did not show any response) showed a slow localized TMS evoked response (2) MCS and LIS showed complex widespread TEPs (3) Effective connectivity discriminates between VS and MCS (4) Patients who recovered from coma showed a change in effective connectivity
Ragazzoni et al. (2013)	5 MCS 8 VS 5 HS	Left or right M1 Sham	32 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 75% MSO)	Amplitude and scalp distribution of TEPs	(1) In 4 MCS patients, ↓ipsilateral and contralateral TEPS, while TEPs were absent in 1 MCS patient. (2) Five VS patients did not show TEPS, while three VS patients showed only ipsilateral TEPs
Gosseries et al. (2015)	3 VS 8 HS	Multiple sites (patient-specific; intact and lesioned cortical regions)	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 140 V/m) Neuronavigation	TEPs (GMFP)	(1) in VS patients, TEPs are only present when preserved cortical tissue is targeted
Formaggio et al. (2016)	4 UWS 1 MCS 5 HS	Bilateral M1	30 channels Sampling rate: 1024 Hz	Single pulse (biphasic, 110% RMT) Neuronavigation	Cortical oscillations (time-frequency)	(1) Opposite pattern of EEG power in alpha and beta bands in patients compared to HS (2) No modifications of slow rhythms (delta and theta) in patients
Casarotto et al. (2016)	81 severe DOC 48 conscious brain injured (5 LIS, 16 subcortical stroke, 18 cortical stroke, 9 EMCS) 102 HS (during wakefulness, NREM sleep, REM sleep, and different kinds of anesthesia)	Bilateral superior frontal gyrus Bilateral superior parietal lobe	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120 V/m) Neuronavigation	PCI	(1) The empirical PCI cutoff first determined in the benchmark population including HS and conscious brain-injured patients resulted in a 94.7% sensitivity in detecting MCS (2) The PCI cutoff could stratify VS patients in three subgroups: no-response, low-complexity, high-complexity
Bodart et al. (2017)	9 UWS 11 MCS 2 EMCS 2 LIS	Bilateral superior frontal gyrus Bilateral superior parietal lobule	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 100–150 V/m) Neuronavigation	PCI	(1) PCI cutoff combined with FDG-PET allowed for congruent classification of 22/24 patients (2) PCI showed high complexity levels in 11 MCS and 4 UWS patients (3) PCI confirmed consciousness in 2 EMCS and 2 LIS patients
Intervention						
Bai et al. (2016)	1 DOC 5 HS	left DLPFC	62 channels Sampling rate: 2000 Hz	Single pulse (monophasic, variable intensity)	TEPs PCI GMFP Pre (T0), post session 1 (T1) and post session 20 (T2): 20 daily 10 Hz rTMS	(1) T0: clinical scale indicates MCS, TEP and PCI indicate VS (2) T1: no clinical improvement and no change in TEP, PCI and GMFP (3) T2: clinical improvement and increase in PCI, TEP and GMFP

Legend: DLPFC: dorsolateral prefrontal cortex; DOC: disorders of consciousness; EMCS: emergence from minimally conscious state; FDG-PET: 18F-fluorodeoxyglucose positron emitted tomography; GMFP: global mean field power; HS: healthy subjects; LIS: locked-in syndrome; MSC: minimally conscious state; MSO: maximal stimulator output; PCI: perturbation complexity index; RMT: resting motor threshold; TEP: TMS-evoked potential; UWS: unresponsive wakeful syndrome; VS: vegetative syndrome.

and medial frontal areas within the default mode network. As results were paralleled to an improvement in episodic memory observed after the rTMS of PC, these neural changes may underline clinical improvements. Similarly, Kumar et al. (2017) explored the plasticity-inducing effect of PAS applied to the DLPFC in AD patients compared with a group of healthy controls. Results showed reduced PAS-induced potentiation of mean cortical-evoked activity in the AD group, suggesting that TMS-EEG can be a marker of altered DLPFC plasticity in AD.

6.2.1.1. Summary and future clinical applications: Alzheimer's disease. The number of TMS–EEG studies in AD and MCI remain limited, with a few studies conducted on small population size. However, results do indicate a clinical potential for the use of the method to better understand the evolution of neurophysiological changes in this neurodegenerative disorder, such as excitability and connectivity alterations. Recent studies on the effect of novel NTBS interventions for AD, i.e., precuneus high-frequency rTMS and DLPFC PAS, have clearly demonstrated the potential of TMS–EEG as a marker of NTBS-induced neural changes and neuroplasticity. Furthermore, TMS–EEG could help shed light onto the effects of pharmacological treatments on cortical excitability and connectivity, such as cholinesterase inhibitors. Given the converging evidence derived from TMS–EMG studies pointing towards altered M1 afferent inhibition (short-latency afferent inhibition) related to cholinergic activity in AD (Cantone et al., 2014), the use of novel TMS–EEG derived measure of SAI (Noda et al., 2015a) in prefrontal regions would be highly relevant in this population. Task-related TMS–EEG is also an interesting avenue of investigation in AD in order to better understand the process underlying memory dys-

functions. Protocols such as the one employed in a recent TMS–EEG study conducted by Rose et al. (2016), where TMS was used to reactivate latent working memories, would be of great interest. Finally, the utility of TMS–EEG in neurodegenerative diseases, such as AD, will require systematic studies to clarify the relative contributions of normative aging and underlying neuropathological processes.

6.2.2. Stroke

Stroke is a debilitating acquired neurological injury and the second leading cause of death in industrialized countries (Lloyd-Jones et al., 2010). Cognitive, motor and language deficits are frequently observed following a stroke. The core of research in this field is to better understand plasticity mechanisms following injury and to learn how to promote recovery by acting on this plasticity. Brain stimulation techniques, such as rTMS and tDCS, are increasingly used as adjuvant therapies to promote plasticity and recovery of symptoms, such as language skills (Kubis, 2016). Current therapies are targeted to ipsi- or contra-lesional areas. TMS–EMG has greatly contributed to the understanding of neurophysiological motor dysfunctions (Dimyan and Cohen, 2010; Di Pino et al., 2014). Despite encouraging findings, there is a lack of objective prognosis markers of efficient treatments in stroke, especially when applied outside of M1, paving the way for the use of new investigative tools such as TMS–EEG. Four studies have employed the technique, one as a marker of treatment in post-stroke aphasia, and three to study the neurophysiology of post-stroke motor dysfunctions (see Table 10). Results are summarized below.

More than 20% of individuals suffering from ischemic stroke will develop symptoms of aphasia, i.e., an impairment of language affecting the comprehension and/or production of speech (Shah et al., 2013). As tDCS was shown to provide a supplementary treatment approach for aphasia when combined with language treatment, Cipollari et al. (2015) assessed the effects of right anodal vs. sham tDCS on TMS–EEG cortical reactivity with concurrent language therapy (i.e., simultaneous melodic intonation therapy). Both the language treatment only (plus sham tDCS) and the combined anodal tDCS and language treatment increased the amplitude of TEPs around 87 ms. Moreover, anodal tDCS combined with the treatment led to an increase of TEPs around 118 ms. Accordingly, behavioral data showed that the language treatment combined with sham and anodal tDCS led to functional improvements, although they were significantly greater following anodal tDCS. Their findings suggest that the underlying mechanisms of functional improvements can be related to changes in cortical reactivity close to the stimulated region and that anodal tDCS may increase the effect of standard treatments.

The neurophysiological mechanisms underlying motor recovery following stroke remain largely unknown; this has impeded the development of efficacious therapies (Kubis, 2016). As stated above, many studies have assessed the use of MEPs as markers of motor recovery following stroke (Smith and Stinear, 2016). However, TMS–EEG may be a more powerful tool for exploring local activity and connectivity changes that occur post-stroke. As such, the TMS-evoked N100 component was used to identify neurophysiological changes in acute post-stroke patients and to assess the relationship with clinical recovery of symptoms (Manganotti et al., 2015). A better prognosis was found to be associated with a reliable ipsilesional N100, even if ipsilesional MEPs could not be elicited. In contrast, less satisfactory recovery was noted when MEPs could be elicited from the lesioned hemisphere but TEPs could not be recorded. The authors suggest that combining both methods can provide a better neurophysiological predictor as they explore different circuits, i.e., the corticospinal tract vs. cortical-subcortical circuits. TMS–EEG was also used to assess the integrity of effective interhemispheric connectivity in chronic stroke (Borich et al., 2016). Specifically, the authors investigated interhemispheric connectivity between the motor cortices in the beta frequency range using the imaginary part of coherency (IPC) during active and resting motor states. Compared to healthy controls, stroke patients showed greater beta IPC values when the ipsilesional M1 was stimulated, suggesting functional reorganization within the motor system after stroke. The fact that this difference was not observed at rest suggests state-dependency of this effective connectivity measure and may reflect involvement of GABAergic activity in post-stroke reorganization.

More recently, Pellicciari et al. (2018) performed a longitudinal study using TMS–EEG to assess the time-course of cortical reorganization after subcortical ischemic stroke resulting in motor symptoms. The affected and unaffected M1 and parietal cortex were stimulated in a sample of 13 patients in the sub-acute phase, assessed 20, 40, 60 and 180 days after stroke onset. EOR, GMFP and TEPs were compared at baseline (day 20) with a group of 10 healthy controls. While no difference was found in the parietal cortex, stroke patients displayed reduced amplitudes of all TEP components and GMFP, as well as reduced evoked oscillatory activity in the alpha-, beta- and delta-band. Longitudinal analyses showed an increase of M1 alpha evoked power and GMFP in the affected hemisphere in comparison with the unaffected hemisphere. Interestingly, the increase in the alpha-band power was associated with clinical improvements, suggesting that alpha activity could be a predictor of motor recovery. These results also point towards the presence of a shift in M1 cortical excitability within the affected hemisphere that could be indicative of neuroplasticity mechanisms. Authors conclude that TMS–EEG is a useful tool to characterize and longitudinally track clinically-relevant changes following stroke.

6.2.2.1. Summary and future clinical applications: Stroke. TMS–EEG studies in stroke are sparse and were conducted only in small samples. Findings suggest the capability of TMS–EEG as a biomarker of treatment effects in aphasia, and a neurophysiological index of plastic changes occurring in the M1 following stroke. TMS–EEG was shown to be a better prognostic measure than TMS–EMG and longitudinally monitor neural changes, again highlighting the clinical prospective of the method among this population, but this will need confirmation in larger study samples. As to future directions, it would be interesting to conduct longitudinal studies in large samples to assess the potential utility of TEPs as an index of outcome prediction and treatment effects.

6.2.3. Parkinson's disease

Parkinson's disease (PD) is a movement disorder characterized by akinesia, rigidity and tremor at rest. The pathophysiology of PD involves a loss of dopaminergic neurons in the *substantia nigra* and is associated with dopamine deficiency in the basal ganglia. Treatment of PD primarily involves levodopa therapy. Deep brain stimulation (DBS) is also increasingly used to alleviate symptoms of PD (Pollak and Krack, 2010). Previous TMS–EMG studies have suggested that both levodopa and DBS can act on M1 intracortical inhibitory circuits in the motor cortex (Berardelli et al., 2008; Udupa and Chen, 2013). Only one study explored the potential use of TMS–EEG as a marker of the effects of both treatments (Table 11).

Specifically, TMS–EEG was used to assess the differential impact of levodopa and of subthalamic nucleus DBS (STN-DBS) on neurophysiological state and connections of M1 (Casula et al., 2017). When applied alone, STN-DBS provoked a selective increase of early TEPs (45–80 ms) as well as of TMS-evoked alpha activity. When applied in conjunction with levodopa therapy, additional increases of later components (~100 ms) and beta activity were observed. The authors suggest that STN-DBS may act on

GABAAR-mediated neurotransmission, as revealed by the modulation of early TEP component, while levodopa may act on GABABRR-mediated neurotransmission, highlighted by the modulation of later TEP components.

6.2.3.1. Summary and future clinical applications: Parkinson's disease. TMS–EEG offers great potential to study the underlying mechanisms of PD treatments, such as levodopa and DBS, but also of rTMS and other NTBS techniques that are increasingly employed as complementary treatments (Benninger et al., 2010; Lefaucheur et al., 2014; Benninger and Hallett, 2015). Given that TMS–EMG has greatly contributed to the understanding of M1 abnormalities in PD (Udupa and Chen, 2013), neurophysiological studies involving TMS–EEG could provide further essential insights. In addition, although it remains to be studied, TMS–EEG could act as a marker of longitudinal neurophysiological changes in PD and also shed light onto the mechanisms underlying levodopa-induced dyskinesias. It could also improve the understanding of the neural mechanisms underlying cognitive symptoms, as well as the involvement of cortical regions outside of M1, such as the cerebellum, which are thought to be involved in the disorder (Ni et al., 2010).

6.2.4. Huntington's disease

Huntington's disease (HD) is a movement disorder associated with corticostriatal dysfunctions caused by the pathological expansion of the triplet cytosine-adenine-guanine (CAG) in the Huntingtin gene (HTT) (MacDonald et al., 1993). It is mainly characterized by motor symptoms, such as chorea and dystonia, as well as cognitive and psychiatric disturbances. Several TMS–EMG studies have shown neurophysiological abnormalities in the primary motor cortex, such as altered cortical inhibition (Berardelli and Suppa, 2013; Philpott et al., 2013). Moreover, EEG studies have contributed to a better understanding of the pathophysiology of the disorder, with recent studies suggesting the presence of altered fronto-striatal response inhibition and neural synchronization (Nguyen et al., 2010; Beste et al., 2011). To this date, only one study explored the potential use of TMS–EEG as a neurophysiological marker of HD (Table 12).

Casula et al. (2018) explored for alterations in the synchronization of neural activity in the motor system (M1 and premotor cortex) in 16 individuals with presymptomatic HD (preHD) who are carriers of the *HTT* CAG mutation, compared with 16 age-matched healthy volunteers. HD mutation carriers showed reduced phase synchronization, as assessed via the ITC index, in the theta and beta bands when M1 was stimulated, while no difference was observed after premotor stimulation. HD mutations carriers also displayed increased TMS-evoked cortical activity around 150–250 ms following stimulation of M1, but not the premotor cortex, as revealed by TEPs and GMFP. In addition, participants that displayed better motor performance at a behavioral motor task (i.e., speeding tapping task) showed greater phase theta synchronization and increased TMS-evoked cortical activity (GMFP). The authors suggest that these abnormalities may reflect impairment of the timing of synchronization and desynchronization of the motor network that can be highlighted in individuals prior to the symptomatic phase of HD.

6.2.4.1. Summary and future clinical applications: Huntington's disease. HD is a neurodegenerative movement disorder involving complex anatomical and biochemical features underlying a myriad of cognitive, motor and behavioral symptoms. In this context, TMS–EEG is likely to provide novel avenues of investigation to better understand neural abnormalities that are present in the motor network, but also in non-motor regions that are affected by the disorder such as frontal regions (Philpott et al., 2013). The only study that employed TMS–EEG to this date has demonstrated that it is a sensitive tool to study neurophysiological alterations in the motor network associated to HD even in the preclinical stage. TMS–EEG could therefore be used to study longitudinally the evolution of neurophysiological alterations in HD. In line with the TMS–EMG literature suggesting abnormal GABAergic cortical inhibition, future studies should explore for cortical inhibition abnormalities in non-motor regions. In addition, TMS–EEG also offers great potential to study the effect of treatments on neural activity.

6.2.5. Mild traumatic brain injury

Mild traumatic brain injury (mTBI) is defined as an acute brain injury that result from mechanical energy exerted to the head from external physical forces (Kristman et al., 2014). Although mTBI has been long considered as a mild injury, recent associations with increased rate of development of neurodegenerative disorders following repeated mTBIs has prompted research on objective markers of possible long-term effects on brain function and prognosis (Lefebvre et al., 2015). Several TMS–EMG studies over motor regions have shown short- and long-term impairments in intracortical inhibition, presumably related to GABAergic activity (Lefebvre et al., 2015). However, other regions have been shown to be more susceptible to external forces than M1. Only two studies have been conducted with TMS–EEG in this population (Table 13).

TMS–EEG was first employed in a multimodal case study to explore for objective neurophysiological markers of recovery following mTBI (Bashir et al., 2012). Specifically, motor-cortex TEPs were assessed in a patient at 2 and 6 weeks post-injury at rest, as well as pre/post a single session of cTBS over M1. At both time points, the mTBI subject showed increased widespread activity at 50 ms when compared with a group of healthy subjects. mTBI was also associated with an abnormal response to cTBS at week 2, as revealed by an increase of this widespread activity, which was not observed at week 6. The authors suggested that TMS–EEG could provide a neurophysiological marker of cortical abnormalities following mTBI.

TMS–EEG responses were investigated by another group in fully recovered and persistently symptomatic mTBI compared to healthy controls (Tallus et al., 2013). This study revealed possible interhemispheric connectivity alterations in the symptomatic group, as revealed by increased interhemispheric latency differences in the M1 P60 induced by increases in TMS intensity, which was not observed in controls. Moreover, the symptomatic group showed delayed ipsilateral DLPFC P30 (vs. controls) and DLPFC N45 (vs. asymptomatic), which may be related to impaired functional connectivity and decreased excitability. Finally, both mTBI groups showed M1 P30 abnormalities compared to controls. The authors concluded that TMS–EEG highlighted long-lasting functional changes in the brain following mTBI, which could differentiate asymptomatic versus symptomatic individuals.

6.2.5.1. Summary and future clinical applications: Mild traumatic brain injury. TMS–EEG offers great potential for studies of mTBI, but evidence is currently lacking with only two small studies being conducted thus far. Longitudinal TMS–EEG studies could greatly improve current understanding of the time course of neurophysiological alterations following mTBI, such as changes in cortical excitation, cortical inhibition and connectivity, and of the relationship with potential development of degenerative disease, e.g., chronic traumatic encephalopathy. Importantly, this could provide an index of those alterations in regions that are thought to be more susceptible to external forces applied to the brain such as temporal, frontal and occipital regions.

6.2.6. Disorders of consciousness

Disorders of consciousness (DOC) result from severe brain injury and are clinically subdivided into (1) unresponsive wakeful-

ness syndrome (UWS) or vegetative state (VS): wakefulness without awareness where patients are eyes-open but unresponsive and capable of reflexive movements only; (2) minimally conscious state (MCS): non-communicating patients who can perform inconsistent, limited voluntary movements as signs of consciousness (Giacino, 2004). The locked-in syndrome (LIS), which involves a complete paralysis of the body with preserved sensory and cognitive function, is not a DOC but often mistaken as one (Gosseries et al., 2014). Diagnosis of DOC is currently based on bedside evaluations which target the observation of non-reflexive behaviors following sensory stimulations or responses to commands. Thus, they are largely dependent upon the integrity of sensory and motor pathways. In this context, TMS–EEG offers great potential because it does not require any active participation from the patient or any language comprehension and is independent of the integrity of sensorimotor pathways (Massimini et al., 2009a; Gosseries et al., 2014; Sarasso et al., 2014). Moreover, TMS–EEG allows for the investigation of effective connectivity, i.e., rapid causal interactions between cortical areas, which is thought to be a prerequisite for consciousness. Six studies have assessed the use of TMS–EEG as diagnostic tool to highlight neurophysiological characteristics of DOC, while one study used TMS–EEG to investigate the effect of rTMS therapy (Table 14). Results are summarized below.

Rosanova and colleagues were the first to use TMS–EEG to detect and track neural correlates of consciousness by evaluating effective connectivity in 17 unconscious patients either in a UWS, MCS, LIS or acute coma (Rosanova et al., 2012). They showed that in UWS patients, TMS triggered a simple local response suggestive of a breakdown of effective connectivity qualitatively similar to the one observed in unconscious healthy individuals during slow-wave sleep (Massimini et al., 2005) or anesthesia (Ferrarelli et al., 2010). MCS patients showed complex TEP activations spreading far from the stimulation site, involving both contra- and ipsilateral regions. In patients in acute coma who spontaneously evolved towards MCS and then emerged from MCS recovering functional communication, a longitudinal follow-up was performed showing specific changes in effective connectivity that preceded behavioral changes. In sum, TMS–EEG measures of effective connectivity showed a clear-cut difference between fully unresponsive patients and patients showing minimal signs of consciousness, and cortical effective connectivity was restored early in sub-acute patients who progressively recovered the ability to communicate.

Similarly, Ragazzoni et al. (2013) aimed at verifying if TEP-based indexes of cortical reactivity and connectivity could differentiate UWS from MCS patients. Compared to healthy controls, all patients showed abnormal TEP responses. However, UWS patients' responses differed from those of MCS patients. Specifically, 4 of the 5 MCS patients displayed present but reduced ipsilateral and contralateral TEPs. While five of the UWS patients did not show any TEP, three displayed responses confined to the stimulated hemisphere. This again suggests that TEPs can be a valid index of the level of consciousness in DOC.

In order to demonstrate that TEPs are genuine cortical responses to direct stimulation and therefore can only be recorded from intact cortex, TMS–EEG was recorded by stimulating several lesioned and non-lesioned areas of the cortex in 3 UWS patients (Gosseries et al., 2015). When TMS was delivered over cortical lesions, stimulation was ineffective and did not produce any EEG response. From a methodological point of view, these results highlight the importance of accurate neuronavigation systems to target preserved cortical regions with TMS when dealing with brain-injured patients in order to get interpretable results. Furthermore, this study shows that TEPs can only be produced when preserved brain areas are targeted, demonstrating that TEPs reflect direct activation of the cortical sources rather than only the activation of peripheral scalp muscles, or auditory and somatosensory responses produced by the click and vibration of the TMS coil.

TMS-induced oscillatory activity has also been assessed as a tool to differentiate UWS from MCS patients (Formaggio et al., 2016). Control subjects displayed early synchronization of slow waves followed by a desynchronization of alpha and beta activity over frontal and centro-parietal electrodes. In patients, early synchronization of alpha and beta was observed over sensorimotor areas without any significant modification of slow rhythms. The authors suggest that these results could indicate a brain state of reduced information processing in patients, as well as a rearrangement of cortical patterns.

The perturbational complexity index (PCI) was also recently studied as a tool to objectively stratify UWS patients and detect MCS patients (Casarotto et al., 2016). To do so, 150 subjects were investigated to determine a PCI cut-off level that discriminates between conscious and unconscious conditions. This group included (*i*) healthy subjects who were either conscious and communicating (wakefulness) or conscious but disconnected (REM sleep and ketamine anesthesia) or unconscious (NREM sleep, anesthesia with Midazolam, Xenon and Propofol) and (*ii*) conscious awake brain-injured patients (stroke, LIS and emergence from MCS). The PCI cut-off empirically estimated from the benchmark population provided a sensitivity of 94.7% in detecting MCS patients, irrespective of the alteration of background EEG according to standard EEG evaluation. This PCI-based assessment applied to UWS patients and revealed a stratification of this clinically homogeneous category into three different subgroups: no-response (about 30%), low-complexity (about 50%) and high-complexity groups (about 20%). Notably, the UWS patients with high-complexity PCI values were also characterized by a better prognostic outcome, suggesting that they may retain a capacity for consciousness that is not expressed in behavior. The authors propose that this PCI-based stratification could eventually help orient further treatments such as rehabilitation programs for high-complexity patients or neuromodulation for low-complexity patients. In a subsequent study, Bodart and colleagues (Bodart et al., 2017) confirmed the clinical usefulness of the PCI cut-off in a population of 24 patients. Indeed, the PCI index revealed high complexity in all patients with recovered consciousness, as well as 10 of the 11 MCS patients. Interestingly, the measure also revealed high complexity of cortical activity in 4 of the 9 UWS patients, again in support of its high sensitivity. Moreover, the authors investigated the concordance of PCI classification with a validated diagnostic tool, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and showed very high congruency (22/24 patients), suggesting that joint measures could be a useful complement for diagnosis of DOC patients.

Previous case studies have shown clinical improvements following rTMS in DOC. However, the assessment of the effects of rTMS is problematic and there is a need to develop reliable objective methods. A recent single case study used TMS–EEG to assess evidence of recovery following a rTMS treatment, consisting of 20 consecutive daily sessions of 10 Hz rTMS applied to the left DLPFC, in a DOC patient diagnosed with a MCS at baseline (Bai et al., 2016). TEPs were also assessed in five age-matched healthy controls. A progressive clinical improvement was observed, accompanied by changes in TEPs amplitude and complexity (i.e., GMFP amplitude and PCI value). Although preliminary, this study suggests that TMS–EEG may be an efficient assessment tool of changes induced by rTMS protocols in DOC.

6.2.6.1. Summary and future clinical applications: Disorders of consciousness. The unique and complex issues involved in assessing levels of consciousness in the absence of behavioral responses are ideally suited to TMS–EEG, which is able to probe thalamocor-

tical circuits in unresponsive states. To this date, TMS–EEG has been shown to be a highly effective in assessing levels of consciousness in DOC and could potentially become part of clinical routine practice, although some technological development is still needed to simplify and standardize the experimental setup. Further studies among large populations of DOC patients could identify if some objective measures, such as PCI, can be reliable diagnostic and prognostic markers. It should be noted that TMS–EEG also greatly contributed to the study of neural substrates of consciousness in healthy individuals, such as during sleep or pharmacologically induced anesthesia, as documented in recent reviews (see (Massimini et al., 2009b, 2012; Sarasso et al., 2014)).

6.2.7. Epilepsy

Epilepsy is one of the most common neurological diseases, resulting in major socioeconomic burden both at individual and societal levels (Moshé et al., 2015). Despite recent advances in genetics and neuroimaging, scalp EEG remains the principal diagnostic modality but suffers from certain limitations. These include a fairly low sensitivity (ranging from 39% to 53% after the first EEG in patients with a single unprovoked seizure and epilepsy, respectively, (Baldin et al., 2014)) and a relative lack of predictive power regarding seizure recurrence or response to therapeutic interventions. These shortcomings limit the ability of scalp EEG to inform decision-making and guide the personalized management of epilepsy in clinical practice.

In recent years, TMS was extensively employed as a non-invasive brain stimulation technique in the field of epilepsy, providing important insight into the pathophysiological mechanisms of epilepsy as well as clinically relevant information. For instance, emerging evidence suggested that the effect of antiepileptic drugs (AEDs) on motor threshold and intra-cortical inhibition could be an early predictor of pharmacoresistance in epileptic patients (Badawy et al., 2007, 2010, 2013).

In the light of the above, it is reasonable to assume that the combination of the two methods, (i.e., TMS–EEG), will prove to be particularly relevant for exploring the pathophysiological substrate of epilepsy and may further increase the diagnostic and prognostic potential of EEG. This hypothesis has been recently addressed in an accumulating number of studies. In focal epilepsy, two studies have used TMS–EEG to characterize TEPs in the epileptogenic focus, whereas four studies have used TMS–EEG to investigate the underlying pathophysiology of genetic generalized epilepsy (GGE). Results are summarized below (see Table 15 for detailed results).

With regards to focal epilepsy, early attempts to activate seizure foci and localize the epileptogenic zone with TMS provided disappointing results due, in part, to technical limitations (e.g. the inability to record reliable EEG signals concurrently with magnetic stimuli). However, the advent of TMS–EEG kindled the interest in this application. In a pioneering TMS-EEG study, Valentin et al. (Valentin et al., 2008) investigated 15 patients with focal epilepsy and a group of healthy subjects. They applied series of single-pulse stimuli at resting motor threshold with a figure-of-eight coil centered over several standard electrode positions. The authors recorded abnormal *late responses*, further subdivided into *delayed responses* (i.e., TMS-induced waveforms similar to spontaneous interictal epileptiform discharges occurring at a latency > 100 ms and < 1 sec post-stimulus) and *repetitive responses* (i.e. new-onset rhythmic activity). Importantly, the late TMS–EEG responses were never observed in healthy subjects (specificity 100%) but were present in 11 out of 15 epileptic patients (sensitivity 73%). It is worth noting that the four patients who did not show late TMS–EEG responses, had deep-seated epileptogenic regions (i.e. at the insular cortex or medial temporal structures). The combined use of scalp EEG and TMS–EEG data demonstrated abnormalities in all patients and these abnormal findings lateralized consistently in 14 out of 15 subjects, thereby supporting the diagnosis of focal epilepsy. The authors concluded that TMS–EEG can reliably identify the epileptogenic zone and may significantly improve the diagnostic approach to epilepsy by providing an earlier and more certain diagnosis. (Pascual-Leone et al., 2011). Shafi et al. (2015) combined TMS–EEG with resting-state functional connectivity MRI (rs–fcMRI) in order to explore cortical reactivity in eight patients with periventricular nodular heterotopia (PNH), a malformation of cortical development associated with focal epilepsy. In PNH, seizures emanate from heterotopic nodules, neocortical areas or both indicating that ictogenesis in this syndrome results from a complex interplay between cortical and subcortical generators. The authors used rs–fcMRI in order to identify neocortical regions with abnormal connectivity to heterotopic nodules (“connected” regions) as well as control “non-connected” regions and then stimulated with single-pulse navigated TMS–EEG both targets so as to explore the pathophysiological significance of the aberrant corticoheterotopic circuits. It was demonstrated that “connected” regions in patients with active epilepsy are characterized by cortical hyperexcitability, as evidenced by an abnormal increase of the normalized GMFP in the late (225–700 ms) part of TEPs. This abnormality was specific to “connected” regions and did not occur in healthy age- and gender-matched subjects. Further, electrical source imaging of spike and seizure onset in one patient co-localized with the generator of abnormal TMS-induced EEG activity. On the basis of these findings, the authors suggested that TMS–EEG could be a useful biomarker of epilepsy in the context of gray matter heterotopias.

With regard to genetic generalized epilepsy (GGE), a number of studies highlighted differences between patients with generalized seizures and healthy control subjects in terms of TEP characteristics. Julkunen et al. (2013) investigated patients with Unverricht-Lundborg Disease (EPM1), a subtype of progressive myoclonic epilepsy, and reported hyperexcitability of M1 as seen through an amplitude increase of the P30 waveform amplitude, suggesting enhanced cortico-cortical excitability, and reduced amplitude of the N100–P180 complex. Additionally, patients showed abnormal evoked oscillatory activity, specifically, reduced power and coherence of alpha and beta oscillations. These results could indicate abnormal cortical inhibition and impairments of cortico-cortico and/or thalamo-cortical connections in EPM1. Del Felice et al. (2011) assessed the effect of sleep deprivation in juvenile myoclonic epilepsy (JME) via TMS–EEG. TEPs were recorded during wake, sleep deprivation and sleep conditions in 10 JME patients and 12 healthy subjects. They observed that sleep deprivation resulted in an increase of late TEP potentials (100 and 180 ms) in both groups. However, this increase was greatly magnified in patients with JME. This study indicates that TMS–EEG is sensitive to cortical excitability changes in both pathological and physiological conditions. Finally, a recent study investigated a group of patients with generalized (n = 11) and focal (n = 2) epilepsies in comparison with healthy subjects (n = 18) with single-pulse TMS (ter Braack et al. 2016). The authors observed an increased amplitude of N100 after left motor cortex stimulation and of the P180 TEP after right motor cortex stimulation with both alterations being localized in the centro-parietal areas. All in all, these studies suggest that patients with generalized epilepsy display shared abnormal cortical reactivity in the late TEP components, i.e., N100 and P180, as well as distinct changes in cortical reactivity that possibly occur in a syndrome-specific manner.

More recently, (Kimiskidis et al., 2017) designed an exploratory, phase II TMS–EEG study with a dual objective. As a first step, the authors sought to optimize a brain stimulation protocol for investigating cortical excitability in patients with GGE. It is well-known that all EEG activating procedures in epilepsy (i.e. hyperventilation, photic stimulation, sleep deprivation, etc.) aim to provoke EDs.

Table 15
Epilepsy.

Authors	Sample	Region(s) of interest	EEG recordings	TMS parameters	Measurements/ Intervention	Main result(s)
Neurophysiology – focal epilepsy						
Valentin et al. (2008)	15 focal epilepsy 15 HS	7 scalp regions	21 channels Sampling rate: NA	Single pulse (monophasic, 100% RMT) Neuronavigation	TEPs (early vs. late responses)	(1) 11/15 patients showed late (delayed) EEG responses, while no HS (sensitivity: 73%, specificity: 100%) (2) Late EEG responses predicted lateralization of epileptogenic region in 8/11 patients (3) 6/9 patients with identifiable epileptogenic region displayed late EEG responses when epileptogenic region was stimulated
Shafi et al. (2015)	8 PNH 8 HS	2 ROI (connected and non-connected)	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 120% RMT	TEPs (spatial, temporal) Source localization	(1) PNH (vs. HS): ↑ late TEPs component amplitudes and ↑ late GMFP (225–700 ms) in connected regions (2) Source localization in 1 PNH patient: convergence with functionally connected region
Neurophysiology – GGE						
Del Felice et al. (2011)	10 JME 12 HS	Left M1	32 channels Sampling rate: 5000 Hz	Single pulse (biphasic, 110% RMT)	TEPs Measured during wake, sleep deprivation and sleep	(1) Sleep deprivation vs. wake, sleep vs wake: important ↑ P100 and N190 amplitude in JME (2) Sleep deprivation vs. wake: small ↑ P100 and N190 amplitude in HS (3) JME vs. HS: ↑ P100 amplitude during drowsiness and sleep; ↑ N190 during sleep deprivation and deep sleep
ter Braack et al. (2016)	13 epilepsy (11 generalized, 2 focal) 18 HS	Bilateral M1	64 channels Sampling rate: 2048 Hz	Single pulse (biphasic, 110% RMT) Neuronavigation	TEPs	(1) left M1: ↑ N100 amplitude (vs. HS) (2) right M1: ↑ P180 amplitude (vs. HS)
Julkunen et al. (2013)	7 EPM1 6 HS	Left M1	60 channels Sampling rate: 1450 Hz	Single pulse (biphasic, 90% RMT) Neuronavigation	TEPs Cortical oscillations (ERSP, ITC)	(1) ↑ P30 and ↓ N100/P180 amplitudes (2) ↓ alpha-, beta- and gamma-band power (3) ↓ ITC in alpha- and beta-bands
Kimiskidis et al. (2017)	25 GGE (13 responders to AEDs, 12 non-responders) 11 HS	Vertex	60 channels Sampling rate: 1450 Hz	Single/Paired-pulse (biphasic, 100% LEThr, ISI: 250 ms) – circular coil	TEPs Signal energy profiles Data mining procedure Measured at rest, during HV and post-HV	(1) TMS evoked EDs in 2 and abnormal TEP morphology in 4 GGE patients (2) GGE: ↑ N30a, N100a and N100b amplitudes and ↑ signal energy in the delta-band (3) Index test: 0.92 (differentiating HS vs. GGE); 0.80 (differentiating responders vs. non-responders)

Legend: AED: anti-epileptic drugs; ED: epileptiform discharges; EPM1: Unverricht-Lundborg disease; GGE: genetic generalized epilepsy; JME: juvenile myoclonic epilepsy; LTEhr: lower epileptogenic threshold; NA: not available; PNH: periventricular nodular heterotopia, ROI: regions of interest.

Accordingly, the relative importance of various TMS parameters was investigated with regard to their ability for inducing EDs. In parallel, however, it was expected that the multi-level analysis of the TMS–EEG data (i.e. descriptive as well as average & single-trial evoked potential analysis) would allow the definition of additional surrogate markers of ictogenicity and thereby improve the sensitivity of the index test. These pilot experiments demonstrated that a circular coil was significantly more effective in inducing EDs compared to a figure-of-eight coil, indicating that a critical mass of brain tissue must be stimulated in order to obtain this activating effect in patients with GGE. The stimulus intensity (SI) level was another parameter of critical importance. The authors followed the standard practice of direct cortical stimulation for the localization of epileptogenic regions (Alexopoulos et al., 2007) by increasing SI until EDs are elicited or a maximum, well-tolerated SI level is reached while taking precautions so as to avoid overstimulation and untoward side-effects. Essentially, this particular protocol aimed at tracking the threshold for eliciting EDs (epileptogenic threshold) rather than fine tune the employed SI level on the basis of motor cortex excitability. As a second step, the final protocol (i.e. a single and paired-pulse TMS–EEG paradigm at rest, during hyperventilation (HV) and post-HV) was applied in a cohort of 25 patients with GGE and a group of age-matched healthy controls (n = 12). The GGE patients were prospectively followed and subdivided into responders (n = 13) and non-responders to antiepileptic drugs (n = 12). Data mining procedures were employed so as to extract a subset of optimal features from TMS–EEG responses which were subsequently given to a Bayesian classifier in order to compute the accuracy of the index test for assigning participants into "patients/controls" and "responders/non-responders" classes. TMS induced EDs in two patients and other morphologically abnormal TEPs in four, all of whom were non-responders to AEDs. The maximal cross-validated accuracy of the index test for differentiating patients from controls was 0.92 (at the post-HV state) and for differentiating responders from non-responders 0.80 (at resting state). On the basis of these data it was concluded that TMS–EEG is a promising diagnostic method in epilepsy and should be further tested as a means to stratify the severity of GGE.

6.2.7.1. Summary and future clinical applications: Epilepsy. The advent of TMS–EEG opened up new avenues for the investigation of epilepsy. TMS may provoke abnormal EEG responses, including EDs, in patients with epilepsy which have significant diagnostic and prognostic implications. In focal epilepsy, TMS-EEG resulted in the reliable identification of the epileptogenic zone and provided evidence of cortical hyperexcitability in grey matter heterotopias that is specifically linked to aberrant connectivity patterns. In GGE, TMS induced EDs provided insight into the pathophysiological

mechanisms of epilepsy. In addition, abnormal TEPs were produced that may be used for the diagnosis of epilepsy, with improved sensitivity and specificity in comparison to currently available techniques, and the prediction of response to treatment with AEDs. Altogether, this highlights the great clinical potential of TMS–EEG in epilepsy. It should be noted that, dependent on the parametrization and the underlying brain state, TMS can exert both activating as well as inhibitory effects on epileptogenic networks. A series of studies that were not reviewed in the present manuscript as they did not employ a typical TMS-EEG paradigm, used EEG to record the acute abortive effect of magnetic stimuli on focal EDs during rTMS (see (Rotenberg et al., 2008, 2009; Kimiskidis et al., 2013; Kugiumtzis and Kimiskidis, 2015). These studies illustrate the utility of rTMS–EEG as a means of monitoring the effects of TMS stimuli on brain epileptiform activity. In addition, they raise the interesting possibility that the acute abortive effect of TMS on EDs may serve as surrogate marker of responsiveness to non-invasive or invasive neuromodulatory techniques (e.g., direct cortical stimulation).

6.3. Challenges and recommendations for clinical TMS–EEG studies

The use of TMS–EEG to study the pathophysiology of psychiatric and neurological disorders is accompanied by a variety of challenges unique to clinical research. In this section, we outline some of those challenges, and provide recommendations for future clinical TMS–EEG studies.

6.3.1. Influence of medications

While pharmaco-TMS has provided a deeper insight into the neural mechanisms underlying the TMS–EEG signal, these studies have also highlighted the potentially confounding influence of medication when interpreting differences in TMS-evoked EEG activity between healthy populations and those with clinical disorders. Given that most clinical populations are taking some form of medication, whereas healthy controls are generally not, differences between groups could simply reflect the effect of the drug as opposed to the pathophysiology of the illness per se. For example, benzodiazepines, which have been shown to increase N45-amplitude and decrease N100-amplitude following M1 stimulation (Premoli et al., 2014a), are commonly prescribed in a range of psychiatric and neurological disorders. The challenge of disentangling medication effects from pathophysiology is common for all clinical studies (Fusar-Poli et al., 2013), not just clinical TMS–EEG. One solution is to test participants both on and off medication, or to test participants who are clinically stable and do not currently require medication. However, there are practical and ethical issues regarding discontinuing medication for research purposes, particularly when the participant may not receive direct benefit from the research intervention and when the risks associated with medication discontinuation are high (Carpenter et al., 1997). Furthermore, long-term medication use can cause changes in brain structure and function, which may be misattributed to the progression of the illness, even if the medication is acutely withdrawn (Fusar-Poli et al., 2013). An alternative to minimize the influence of long-term medication use is to test participants in the early stage of the illness when they are medication naïve, or to test those at high-risk of developing the illness (e.g., family members). While these participant groups can be challenging (both to find and to test), accumulating evidence in relation to medication status is important to determine to what extent TMS–EEG measures indicating illness pathophysiology are confounded by medication.

An additional consideration is the potential for certain medications to alter the seizure threshold (Rossi et al., 2009). While few confirmed seizures have occurred following single or paired-pulse TMS paradigms, rTMS paradigms, such as those used to assess plasticity and for treatments, carry a higher seizure risk. As such, careful consideration is required in the planning, participant screening, execution and environment in which clinical TMS–EEG studies are performed.

6.3.1.1. Recommendation. Where possible, TMS–EEG outcome measures that indicate illness pathophysiology should be confirmed in different illness stages and in groups both on and off medications. Clinical TMS–EEG studies should be performed with extra caution in those taking medications that alter the seizure threshold even when TMS safety guidelines are taken into account (Rossi et al., 2009).

6.3.2. Coil position, stimulation intensity and control conditions

TMS–EEG outcome measures are highly sensitive to stimulation parameters, such as coil position/angle relative to the underlying anatomy, and stimulation intensity (Casarotto et al., 2010). Numerous clinical disorders are associated with changes in brain anatomy which have the potential to influence these parameters. For instance, changes in grey matter thickness can alter scalp-to-cortex distance, which could in turn impact the required stimulation intensities to sufficiently activate the brain with TMS. As such, it is important to control for potential differences in underlying anatomy wherever possible to ensure that different groups and individuals receive comparable stimulation (Casarotto et al., 2011). In regions where TMS results in a clearly defined output, such as the motor (MEPs) or visual (phosphenes) cortex, coil position and stimulation intensity can be easily defined and titrated to ensure equivalence between groups (e.g., using the motor hotspot approach to locate M1 and to determine optimal E-field orientation and intensity when determining resting motor threshold) (Rossini et al., 2015). However, the vast majority of cortical regions do not result in such easily measurable outputs. There are currently no established TMS–EEG measures for setting coil position or stimulation intensity outside of the motor and visual areas. Such methods are urgently required. Stereotactic neuronavigation remains the 'gold standard' for localizing TMS coil position in non-motor/visual regions based on individualized anatomy (Massimini et al., 2005). These methods are particularly useful in pre/post or repeated measure designs where a small change in the positioning of the coil may considerably affect results by enhancing the variability in the output (Harquel et al., 2016). However, this method requires dedicated equipment and can come with the added costs associated with acquiring MRI scans for all participants, although neuronavigation software typically allows for the use of a standard MRI template that can be adjusted to the specific physiology of the participant's head. The other common approach includes using scalp-based landmarks, such as EEG electrodes, to decide the stimulation site. This approach can be useful at the group level, especially when validated against anatomical scans for specific targets (Fitzgerald et al., 2009b; Rusjan et al., 2010). However; it remains limited at the individual level due to anatomical variability.

Stimulation intensity is often set based on RMT obtained in the M1 regardless of the stimulation site. However, the validity of this practice has come in to question (Stokes et al., 2005). Some neuronavigation systems take into account individual anatomy to predict the E-field generated by TMS in the underlying cortex (Casarotto et al., 2011). Adjusting the stimulating E-field intensity and direction based on such modeling offers a method for standardizing stimulation dose in non-motor regions. However, the accuracy of this approach may require further validation for TMS–EEG studies.

Currently, most experiments use auditory masking and/or foam to help minimize sensory inputs to TMS-evoked EEG activity. This approach, together with the application of stimulation parameters able to elicit prominent cortical responses to TMS at the stimulated site, allows to successfully collect genuine brain potentials with likely negligible contribution from sensory-related confounding

factors (Gordon et al., 2018a). On the other hand, the application of sham conditions might be a valuable strategy to eventually subtract multisensory components, thus recovering the genuine cortical activation induced by TMS. However, this approach cannot be applied to non-collaborating patients in whom psychophysical parameters of sensory perception cannot be collected.

6.3.2.1. Recommendation. Where possible, stereotactic neuronavigation should be used to standardize the intensity and orientation of the induced E-field based on individual anatomy. Stereotactic neuronavigation is also recommended for coil position in the case of repeated measure designs to ensure stable positioning among separate sessions. In addition, the pulse duration and waveform should be taken into account to make different pulse waveforms comparable to each other. The planning of stimulus targeting may be based on task-related activation (determined by fMRI), anatomical connectivity (from diffusion-tensor tractography), and/or functional connectivity (e.g., from. by resting-state fMRI data), especially when stimulating brain areas outside of the motor cortex. Given the uncertainty regarding methods for standardizing stimulation intensity in non-motor regions, measures which could influence stimulation intensity, such as scalp-to-cortex distance at the site of stimulation, should be reported if E-field modeling is not possible. On-line inspection of TEPs during the recording and estimation of the signal-to noise ratio is also crucial to ascertain that TMS is effectively delivered on the cortical surface. Finally, whenever the use of sham conditions is required, it would be important to develop carefully designed experimental strategies to accurately reproduce the indirect sensory activity resulting from TMS.

6.3.3. Standardized pre-processing analysis pipelines

As discussed in Section 3, TMS results in a number of artifacts in EEG recordings, which can require specialized analysis pipelines for adequate removal, therefore uncovering the underlying neural activity. Until recently, there was no dedicated software available for TMS–EEG analysis, meaning that specialized analysis was primarily performed using in-house code. The specific analysis steps used to clean TMS–EEG data (Casula et al., 2017a), and the order of these steps (Rogasch et al., 2017) can influence the final TEP. Provided that the same pipeline is used to compare groups within a study, this is not a limitation in itself *per se*. However, the verification of potential pathophysiological mechanisms or biomarkers identified using TMS–EEG requires within- and between-group replication. As such, it is important that standardized pipelines and analysis metrics are established and used between studies and groups. The development of open-source TMS–EEG analysis software has gone some way to address this issue (Atluri et al., 2016; Rogasch et al., 2017). However, a consensus on the most appropriate analysis pipelines for TMS–EEG has yet to be reached. Studies comparing and validating different methods on TMS–EEG artifact removal are required.

6.3.3.1. Recommendation. The analysis pipelines and metrics used in clinical TMS–EEG studies should be described in sufficient detail to allow replication of the methods by other groups, and in keeping with the open science approach, these should be made available to all researchers. The cleaning and preprocessing analysis code used on the data should also be published with any research article to allow full and accurate replication. This is essential to push the field forward and encourage replication studies, which are currently lacking.

6.3.4. Standardization of post-processing analyses

One advantage of the TMS-EEG technique which can also work against the field is the wide choice of post-processing analyses available; any EEG analysis available can be applied to TMS-EEG data. This introduces a very large heterogeneity in results. As such, one important aspect to develop for the advancement of the field is a more standardized approach when reporting and characterizing TMS-evoked responses. For instance, the widely different approaches in reporting results are currently limiting the generalization of results across studies. For example, it is currently difficult to provide a standard characterization of TMS-evoked responses in non-motor regions, despite the growing number of studies. This can be at least partially explained by the major differences in the choice of analysis. For example, some studies report TEP characteristics such as component amplitudes, while other only report GMFP/LMFP characteristics or oscillatory characteristics.

This factor also greatly limits the reproducibility of results, which is essential to the use of TMS-EEG as a clinical tool. Most of the clinical studies reported in this review are conducted in a small sample, with highly specific analyses. Importantly, the majority of studies have never been replicated by other groups.

6.3.4.1. Recommendation. Given the above limitations, we recommend that studies publish all source code used for post-processing of TMS-EEG results, thereby allowing direct replication of comparisons in future studies. As for pre-processing, the development of a post-processing pipeline would greatly contribute to the reproducibility of results. We therefore recommend that the field develops a standardized post-processing analyses template in order to facilitate reproducibility and help develop consistent measures of TMS-EEG activity in specific brain regions. Such a pipeline could include standard measures capturing: (1) main TEP components; (2) spatio-temporal distribution of TEPs; (3) GMFP/LMFP analyses; (4) TMS-evoked oscillations (i.e., ERSP). From this basic post-analysis template, more sophisticated analyses could be applied to EEG data. Finally, we recommend the publication of replication studies in large sample sizes.

7. Conclusions and future directions

TMS–EEG has been shown to be an extremely promising technique to improve our ability to non-invasively probe brain function in healthy and disease states, providing reliable, objective, and quantifiable information related to excitation, inhibition, oscillatory neuronal activity, connectivity, and plasticity. In healthy populations, the studies highlighted in the current review have shed light into neurophysiological properties of cortical areas using standard TMS paradigms of cortical inhibition and excitation, such as LICI and SAI, in motor regions but most importantly also in non-motor cortical regions, such as the DLPFC, which is critical to the pathophysiology of several clinical disorders, as well as cognitive and emotional processes. Pharmaco-TMS–EEG has enabled a better understanding of the neurophysiology underlying the TMS-evoked activity, such as the demonstration of changes in connectivity between regions during various states of consciousness and the modulation of the amplitude of specific TEP components amplitudes by pharmacological agents. Notably, these studies provided important insights into the involvement of GABAergic inhibitory transmission underlying TEPs in M1 and in prefrontal regions, offering a pivotal methodological step towards investigating the dysfunction of the GABAergic systems in neuropsychiatric diseases with TMS–EEG. As such, TMS–EEG also provides an objective tool to systematically assess the efficacy of NTBS protocols in non-motor brain areas, for which the current approach is to use parameters identical to the ones employed in M1. This could also lead to improved, safer and optimized NTBS treatments (e.g., rTMS and TBS) for clinical populations.

Results from the 48 reviewed clinical studies published since 2008 have shown that TMS–EEG is a highly valuable tool to

examine the biological deficits underlying disorders affecting the brain such as SCZ, mood disorders, autism spectrum disorders, Alzheimer's disease, stroke, mild traumatic brain injury and disorders of consciousness. For example, converging results suggest the involvement of abnormal prefrontal N100, LICI and gamma oscillations in SCZ (Ferrarelli et al., 2008, 2012; Farzan et al., 2010a; Canali et al., 2015; Radhu et al., 2015, 2017; Noda et al., 2017a), corroborating the notion of a GABAergic dysfunction, which could become a biomarker of the disorder and a cortical target for therapeutic intervention (Rogasch et al., 2014). TMS–EEG measures were also successfully utilized as predictors of treatment response. In mood disorders, TMS–EEG neurophysiological measures were shown to predict remission following MST (Sun et al., 2016) and to predict patients' response to chronotherapy (Canali et al., 2014, 2017), and as a potential marker of the effects of ECT (Casarotto et al., 2013) and prefrontal TBS (Pellicciari et al., 2017a) on cortical activity. Likewise, TMS–EEG has been shown to be a critical tool in the search for reliable objective neurobiological markers in disorders of consciousness; it can directly contribute to diagnosis and prognosis. The recent development of the PCI index (Casali et al., 2013) and its validation among DOC patients (Casarotto et al., 2016; Bodart et al., 2017) suggests that this novel technique has a clear potential to be directly translated into clinical practice in the upcoming years. TMS-EEG was shown to be a useful biomarker of epilepsy, via the activation of the epileptogenic foci (Valentin et al., 2008; Shafi et al., 2015) and the characterization of abnormal cortical reactivity in different types of GGE. The combination of rs-fcMRI and TMS-EEG to better understand connectivity alterations in focal epilepsy (Shafi et al., 2015), highlighted how the use of TMS-EEG in conjunction with other neuroimaging techniques holds great clinical prospective.

As studies presented in the current review underscored the tremendous potential for clinical applications of TMS–EEG, substantial work is still needed to develop translational biomarkers of diseases that could be used as predictive, diagnostic and prognostic tools, as well as novel targets for therapeutic interventions, and biomarkers to monitor treatment effects. Much of future work should focus on the replication of findings, which is essential to a better understanding of the reliability of TMS–EEG neurophysiological markers of brain disorders. This could be realized via the development of large multi-centre prospective studies. Future investigations should also focus on using TMS–EEG measures to monitor the efficacy of treatments such as pharmacotherapy and psychotherapy in clinical populations (Kaskie and Ferrarelli, 2018). Developing individualized treatments through TMS–EEG is also a highly interesting avenue via, for example, the study of the optimal duration of rTMS treatment in individuals with major depression. Thus far, clinical studies have shown that TMS–EEG can be applied to a large variety of clinical populations in the field of neurology and psychiatry. However, most of the work has been focused on SCZ, depression and disorders of consciousness, as well as on epilepsy. TMS–EEG could contribute to a better understanding of the pathophysiology of many other clinical disorders when used to investigate the function and integrity of brain circuits, such as in chronic pain (Barr et al., 2013), developmental disorders, dementias, and so on.

It should be noted that there are other interesting uses of TMS–EEG that were not explored in the current review. Firstly, rTMS can be combined with EEG (rTMS-EEG) to better understand the effect of repetitive stimuli on ongoing brain activity, which was highlighted in a series of studies in epilepsy where rTMS can be used to abort epileptic activity monitored via EEG (see (Kimiskidis, 2016) for review). This can be particularly relevant to monitor the safety of NTBS paradigms in clinical populations, as well as to individualize NTBS treatments in order to optimize efficacy. In addition, EEG can be employed to guide subsequent TMS intervention (EEG–TMS) (see (Thut et al., 2017) for review). This is particularly relevant to NTBS interventions where EEG-TMS can help to efficiently interact with ongoing neural processes (i.e., when and how to stimulate) in order to optimize the after-effects of the intervention on behavior, and possibly reduce the inter- and intra-individual variability inherent to these techniques (Thut et al., 2017). To do so, EEG-TMS can be used to time the stimulation of a neural target to specific oscillatory states (e.g., high excitability states (Zrenner et al. 2016)), to tune the frequency of a NTBS intervention to a specific frequency of oscillatory activity (e.g., (Thut et al., 2011)), and to time TMS to already entrained cortical oscillations (e.g., (Ruhnau et al., 2016)).

Finally, in order to exploit the full clinical potential of the technique, substantial work is needed to better characterize the broad variety of outcome measures of TMS–EEG. Neurophysiological and pharmacological work in healthy controls will continue to help develop the technique and improve our understanding of the involvement of several brain circuits in the TMS-evoked EEG response (Rogasch and Fitzgerald, 2013; Ziemann et al., 2015). Translational animal studies are also needed to further our understanding of the underlying neural processes of TMS-EEG measures. In addition, standardization of TMS–EEG methodology and data processing is an essential step to promote its use in the scientific community. This would in turn facilitate and promote multi-site investigations (Atluri et al., 2016). The widespread use and refinement of open-source analysis software, such as the recently developed TESA software (Rogasch et al., 2017) and TMSEEG toolbox (Atluri et al., 2016), will definitively help improve reliability and generalization of results, and therefore contribute to the advancement of the TMS–EEG field and its translation to clinical practice.

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