15 Cortical Excitability, Plasticity and Oscillations in Major Psychiatric Disorders: A Neuronavigated TMS-EEG Based Approach

Mario Rosanova, Simone Sarasso, Marcello Massimini, and Silvia Casarotto

15.1 Corticothalamic Oscillations and Psychiatric Disorders

Brain functions critically depend on the interactions between functionally specialized neural structures, encompassing cortical areas and thalamic nuclei [1]. In this framework, information processing within local circuits and communication at distance are thought to be reflected by rhythmic and coordinated fluctuations of excitability [2]. These oscillations emerge from the interactions between local intrinsic neuronal properties and structural connectivity, and play a key role in perceptual, motor and cognitive functions [3]. For instance, oscillations of neural circuits distributed over frontal and parietal cortices have been related to working memory functions [4, 5]. During working memory tasks, fronto-parietal circuits generate electrical oscillations at different frequency bands, each playing a specific role. As such, gamma-band oscillations seem specifically involved in active retaining of information while theta-band oscillations may specifically be involved in ordering items over time, with alpha-band oscillations being mostly involved in the inhibition of task-irrelevant information [6].

M. Rosanova (✉)
Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy

Fondazione Europea per la Ricerca Biomedica Onlus, Milan, Italy
e-mail: mario.rosanova@unimi.it

S. Sarasso · S. Casarotto
Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy

M. Massimini
Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy

IRCCS Fondazione Don Gnocchi, Milan, Italy

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Oscillatory properties of cortical circuits have been classically studied by means of non-invasive techniques, such as EEG. Since its introduction by Hans Berger almost a century ago [7], the EEG has become an essential tool for investigating the relationships between brain rhythms and neuropsychiatric disorders. In psychiatry research, EEG recordings are traditionally performed either at rest or when subjects are engaged by sensory stimuli (Event-Related Potentials—ERPs), motor or cognitive tasks ("cognitive probes").

Such EEG and ERP approaches have revealed abnormal cortical oscillatory patterns in many psychiatric disorders [8, 9] and some of them have been linked with specific cognitive deficits [10, 11]. For example, working memory deficits in schizophrenic patients were found to be associated with reduced prefrontal cortical gamma-band oscillations [12], whereas patients affected by major depressive disorder (MDD) showed left/right asymmetries in the topographical distribution of the alpha-band oscillations [13].

Recording of the ongoing EEG provides valuable information about the oscillatory properties of cortical circuits under different conditions. However, spontaneous brain rhythms are difficult to control even in standardized conditions, and may radically change depending on the experimental conditions, such as fluctuation in the state of vigilance and the level of attention. A classic example is represented by the drastic changes in EEG topography and power that rapidly occur upon eye closing. In relation to psychiatric patients, all these factors are even more difficult to control.

A more reliable assessment of the intrinsic oscillatory properties of cortical circuits can be obtained by measuring steady-state-evoked responses. In this case, visual flashes, or auditory tones, are presented at different rates, and the stimulation frequency that results in the largest EEG or the magnetoencephalography output, the resonance frequency, is detected. This standardized approach yielded consistent results and demonstrated the existence of clear-cut resonance frequencies in specific parts of the human corticothalamic system, around 10 Hz in the visual cortex and around 40 Hz in the auditory cortex. However, steady-state responses, as other responses evoked by the stimulation of peripheral receptors, can only probe a limited set of primary sensory cortices [14–18].

In the following, we will focus on an alternative electrophysiological method to study the oscillatory properties of cortical circuits, i.e. the combination of TMS and EEG. Aided by neuronavigation, TMS-EEG allows to directly perturbate a wide range of cortical areas (including frontal and posterior association cortices) and to record the ensuing electrical oscillations. This technique may thus offer a standardized way of mapping the oscillatory properties of the cerebral cortex in a way that is not dependent on the level of the subject's engagement, and not, restricted to the exploration of sensory areas, two features that seem particularly valuable in the case of psychiatric patients.

15.2 A Short Introduction to TMS-EEG

TMS is based on the physical principle of electromagnetic induction, which was discovered by Faraday in 1831. In the case of TMS, when a strong and short-lasting electric current passes through a TMS coil applied over the scalp, a brief but strong

magnetic field (duration: 1 ms; intensity: 1–2 T) is generated. This magnetic pulse locally depolarizes axonal membranes, leading cortical neurons under the TMS coil to fire action potentials [19, 20]. Then, the synchronous volley of action potentials triggered in the target area by the TMS pulse is conducted down the existing anatomical pathways, such as the corticospinal tract, the activation of which results in a motor evoked potential that can be recorded by combining TMS with electromyography (TMS-EMG) [21, 22]. A similar mechanism leads to the activation of corticocortical and corticothalamic tracts, resulting in local and remote cortical electrical waves and oscillations that can be captured by employing TMS-EEG. Thus, TMS-EEG allows observing the electrical oscillations generated by the thalamocortical circuits activated upon a direct perturbation of a given cortical area.

Due to the large electric field generated by the TMS pulse, its combination with EEG required the development of dedicated TMS-compatible EEG amplifiers. The earliest attempts in this direction trace back to 1989, when Cracco and colleagues measured transcallosal responses by targeting TMS over the primary motor cortex [23]. A few years later, the same group recorded the response of the cerebral cortex to cerebellar magnetic stimulation [24]. However, since a traditional EEG amplifier was employed, these pioneering studies were still strongly limited by large artifacts related to the TMS pulse, and that did not allow to record the immediate responses at the EEG leads under the coil. The first fully TMS-compatible EEG amplifiers were implemented almost 20 years ago [25, 26] and, by obliterating the large and long-lasting electromagnetic artifact induced by the TMS coil discharge, allowed the reliable recording of artifact-free TMS-evoked potentials (TEPs) under the coil a few milliseconds after the TMS pulse [25, 27, 28]. More recently, DC-amplifiers provided with a wide dynamic range and high sampling rates (≥5 KHz) have been employed to successfully record TEPs devoid of long-lasting pulse artifacts [29].

Besides the electromagnetic artifact, spurious and unspecific biological activations may still contaminate the EEG response to TMS. A major challenge is represented by the high-amplitude scalp muscle artifacts that can be triggered by the TMS pulse when areas below cranial muscles are targeted [30]. Second, the sound (TMS "click") and the vibrations produced by the TMS discharge can evoke sensory evoked potentials, which can be effectively abolished by employing a masking noise reproducing the time-varying frequency components of the TMS "click" [28] and by placing a layer of foam between the TMS coil and the subject's head [31]. In order to control these confounding factors, one can follow different approaches, such as performing control experiments that employ sham conditions [32, 33] or removing the artifacts by means of off-line data preprocessing procedures [34]. A third and more dependable approach relies on a real-time quality check of the TMS-EEG signals. Crucially, after choosing a cortical target based on the neuronavigation system and before starting the measurement session, the operator must apply all the available procedures to minimize the possible confounding factors due to the sensory co-stimulation and to maximize the effectiveness of the TMS pulse on the cerebral cortex [35]. First, the parameters of the masking noise, such as the volume of the audio output, should be adjusted in order to effectively mask the TMS "click". In the same vein, the very large early

biphasic deflections due to the direct activation of scalp muscles can be reduced or abolished by changing the orientation of the coil [30]. Finally, the stimulation parameters (coil rotation and stimulator output) should be fine-tuned in order to record TEPs with a good signal to noise ratio and characterized by stimulation site-specific topographies [36]. The employment of a neuronavigation system can help in keeping the selected stimulation parameters constant within and across sessions in the case of longitudinal studies [37].

Once the electromagnetic artifacts evoked by the discharge of the TMS coil are properly managed [36, 38] and generating spurious and unspecific cortical responses to TMS, namely the ones associated with auditory or somatosensory stimulations that are appropriately reduced or abolished, TEPs reflect genuine responses of cortical circuits to TMS [39]. In this way, TEPs can be used to reliably keep track of cortical excitability and intrinsic oscillatory properties of human thalamocortical circuits in both research and clinical settings [40, 41].

The very early components (waves) of TEPs reflect the immediate neural responses of the circuits that are underneath the stimulator and hence are directly excited by the TMS pulse. Therefore, measuring the slope and amplitude of those very early waves of TEPs (10–30 ms) is a dependable way to assess cortical excitability and its changes, i.e. cortical plasticity. This approach, which closely matches the one used in animal studies of cortical plasticity [42, 43], allowed the observation of plastic changes of cortical circuits during wakefulness [44, 45], after a protocol of induction of cortical plasticity via rTMS [46], to compare the effects of single and paired-pulse TMS [47], during and after anodic stimulation with Transcranial Direct Current Stimulation [48, 49], and after the administration of L-DOPA in patients suffering from Parkinson's disease [50] (Fig. 15.1).

To measure cortical excitability and plasticity through TMS one should focus on single components of TEPs, such as the waves that immediately follow the TMS pulse. On the other hand, analyzing the sustained EEG oscillations triggered by TMS can help to better understand the intrinsic oscillatory properties of corticothalamic circuits in healthy and diseased brains. For instance, a TMS-EEG study conducted in healthy subjects showed that different corticothalamic modules oscillate at a preferred "natural" frequency when perturbed by TMS. Specifically, TEPs were consistently dominated by EEG oscillations in the alpha band (8–12 Hz) after stimulation of the occipital cortex (Brodmann area 19), in the beta-band (13–20 Hz) after stimulation of the parietal cortex (Brodmann area 7), and in the fast beta/gamma-band (21–50 Hz) after stimulation of the premotor cortex (Brodmann area 6) [51]. Interestingly, the study also showed that each cortical area tends to oscillate at its own natural frequency, even when it is indirectly activated after the discharge of a TMS pulse over a remote, yet connected cortical area (Fig. 15.2). A further modeling study suggested that the connectivity pattern of each cortical area is a key factor in determining its natural frequency [52]. Along with the evidence that the lesion of thalamic nuclei specifically disrupts TMS-EEG oscillations [53], these studies suggest that the natural frequency is a measure of the intrinsic properties of corticocortical and corticothalamic connections.

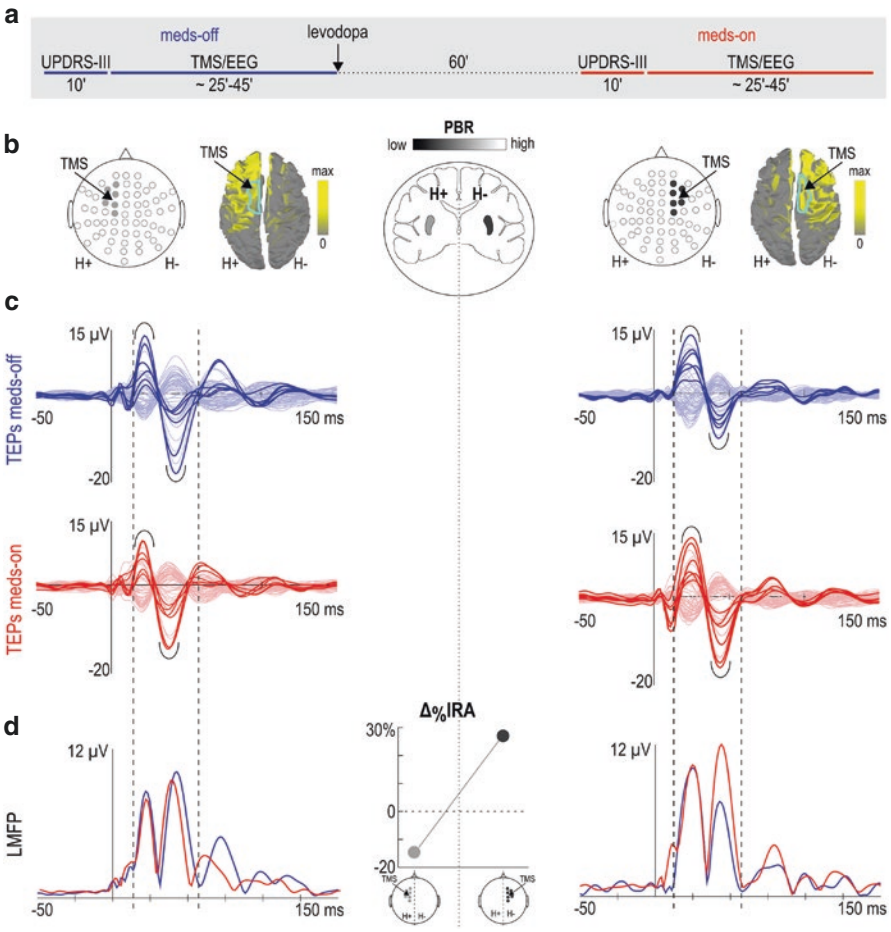

Fig. 15.1 TEPs recorded in patients affected by Parkinson's disease. L-DOPA intake (meds-on) induces a significant increase of the amplitude of the very early components of TEPs in the hemisphere more affected by the degeneration of the basal ganglia circuits (H+), greater than in the less affected hemisphere (H−). Panel **a** shows the overall EEG channel layout with the selected clusters of channels close to the targeted frontal area (cyan contours on the brain maps). Panel **b** shows the butterfly plots of the TEPs recorded at all 60 EEG channels (blue traces in the meds-off condition; red traces in the meds-on condition). U-shaped traces indicate the positive and negative early components of TEPs. Panel **c** shows the Local Mean Field Power (LMFP) and the percentage values of the area under the curve (between the two local minima and encompassing the early consecutive positive and negative waves triggered by TMS; Immediate Response Area: IRA) in the meds-on and meds-off conditions. (Modified from [50])

15.3 TMS-EEG Studies of Major Psychiatric Disorders

Cortical excitability and plasticity in psychiatric disorders have been studied mainly by employing TMS-EMG [54]. This technique has also been employed to assess changes

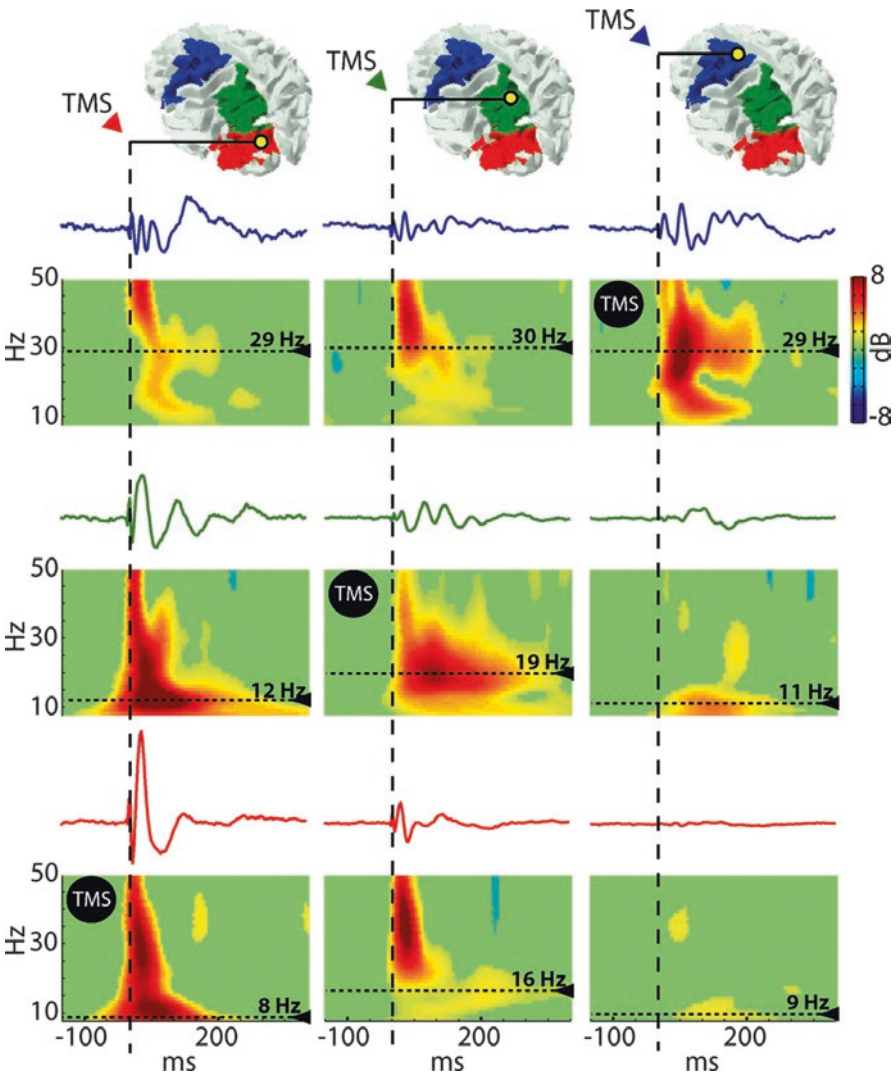

Fig. 15.2 The natural frequency is a local property of individual corticothalamic modules. In the top row, the colored patches on the cortical surface mark the areas from which cortical currents are recorded after the reconstruction of the cortical source activations. Below, time series and Event-Related Spectral Perturbation (ERSP) plots of local cortical currents are displayed for the premotor cortex (first row, blue traces, Brodmann area 6), the posterior parietal cortex (second row, green traces, Brodmann area 7), and the occipital cortex (third row, red traces, Brodmann area 19), when the occipital cortex is stimulated (first column), the posterior parietal cortex is stimulated (second column) and the premotor cortex is stimulated (third column). The dotted lines highlight the peak frequency for each plot. The comparison of the ERSP plots on the diagonal line (marked by the TMS icon) reveals that each cortical area responds with a distinctive natural frequency when directly stimulated. Comparing the plots on the horizontal and on the vertical lines reveals that the natural frequency is a local, intrinsic property that is partially preserved also when its cortical generator is not directly stimulated. (Modified from [51])

due to pharmacological treatments in psychiatric patients [55]. However, TMS-EMG provides indirect measures of cortical excitability and plasticity, as it measures responses to TMS of the corticospinal tract rather than direct responses of the corticocortical and corticothalamic circuits. Most importantly, the use of TMS-EMG is by definition limited to the primary motor cortex, whereas pathophysiological underpinnings of psychiatric disorders mostly involve non-motor cortical regions, such as the prefrontal cortex.

At odds with TMS-EMG, neuronavigated TMS-EEG allows the direct measurement of cortical excitability and plasticity of virtually any cortical area. Moreover, TMS-EEG can provide a read-out of the oscillatory properties of corticothalamic modules without necessarily relying on cognitive probes, i.e. without engaging the subject in a cognitive task. By virtue of these technical advantages, in recent years, neuronavigated TMS-EEG has been employed in psychiatric research to identify possible electrophysiological biomarkers and to study the neurophysiological underpinnings of psychiatric disorders (for recent reviews on the use of TMS-EEG in psychiatry research, see [56–58]).

In a series of TMS-EEG studies conducted in schizophrenic patients, Ferrarelli and coworkers measured the early components of TEPs, and observed a significant reduction of excitability of the primary motor cortex [59] and of the premotor and prefrontal cortical areas [60, 61] in patients compared to healthy controls, whereas parietal cortical areas showed preserved levels of excitability. On the other hand, applying some of the methods used in the studies cited above to measure cortical excitability by means of TMS-EEG, a recent study observed plastic changes in the cortex of patients affected by drug-resistant MDD after treatment [62]. Specifically, in this study, the slope and amplitude of early TEP components, recorded over the premotor cortex, increased after the application of Electroconvulsive Therapy (ECT) in MDD patients compared to baseline (Fig. 15.3). In a similar study, by measuring the slope and amplitude of early TEP waves, an increase of cortical excitability was observed after light therapy and sleep deprivation in the prefrontal cortex of MDD patients [63].

Other research groups focused on specific cortical areas and used TMS-EEG to study the electrophysiological properties of those areas. One relevant example is the dorsolateral prefrontal cortex (DLPFC), which underpins high cognitive functions and plays a key role in the pathophysiology of major psychiatric disorders [64]. In a recent paper, Daskalakis and his coworkers performed TMS-EEG measurements by targeting DLPFC in MDD patients and, compared to healthy controls, observed a larger early TEP negative component named N45, whose amplitude was reliably predicting the state of the patients [65]. In another study, the same group found an altered modulation of the TEP positive component named P60 that correlated with the cognitive impairments in schizophrenic patients [66]. Notably, as both N45 and P60 are thought to be markers of the excitation-inhibition balance in the targeted cortical area, these studies suggest that TMS-EEG measurements can provide further insight into the pathophysiology of MDD and schizophrenia.

TMS-EEG has also been employed to investigate the oscillatory properties of corticothalamic circuits in major psychiatric disorders. In a TMS-EEG study on schizophrenia [59], TEPs were recorded by targeting different cortical sites, such as parietal, motor, premotor, and prefrontal areas in schizophrenic patients and healthy

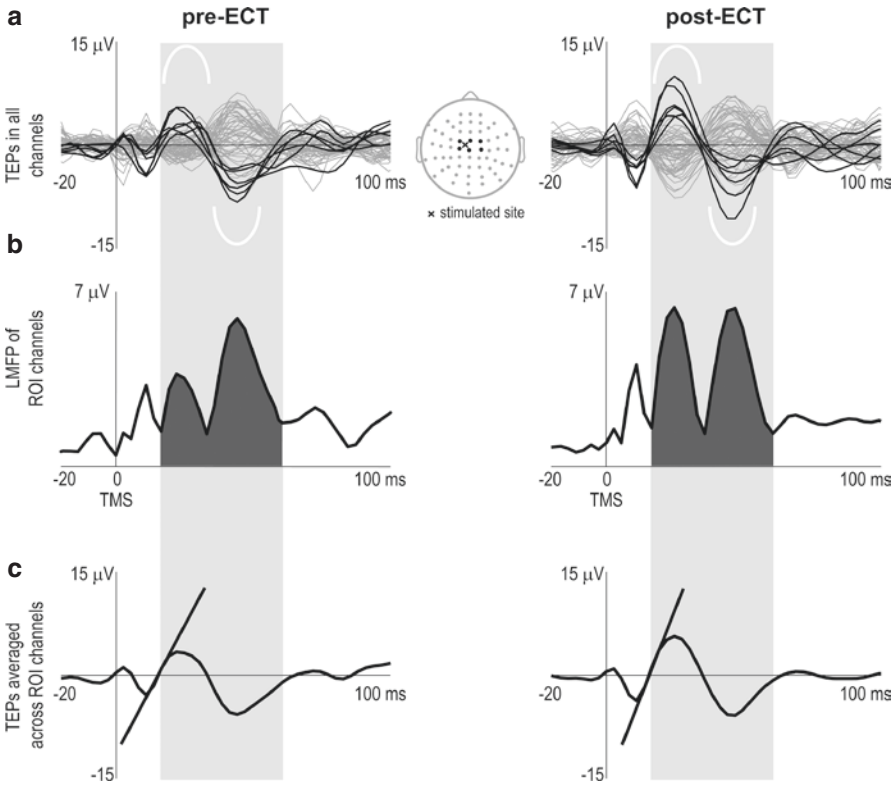

Fig. 15.3 Estimation of cortical excitability after Electroconvulsive Therapy (ECT) by means of TMS-EEG. Panel **a** represents the butterfly plots of the TEPs recorded at all EEG channels before (pre-) and after (post-) ECT. The central map depicts the EEG electrode layout (black and gray dots) on the scalp. Black traces correspond to selected channels (channels from the Region Of Interest; ROI), located nearby the stimulated site (black cross) and containing a large, early TEP component, consisting of a positive wave (white reversed U-shaped trace), followed by a negative wave (white U-shaped trace). Panel **b** reports the LMFP computed considering the channels in the ROI. Cortical excitability was measured by calculating the area (dark gray shadow) between the two local minima (light gray shadow) and encompassing the early consecutive positive and negative waves triggered by TMS (Immediate Response Area: IRA). Panel **c** shows the TEPs averaged across the ROI channels in the two conditions. Slanting lines highlight the slope of the rising side of the early large positive wave evoked by TMS (Immediate Response Slope: IRS). (Modified from [62])

controls. TEPs were then analyzed in the time-frequency domain in order to measure the natural frequency [51] for each cortical site in the two populations. These results further supported the idea that in healthy subjects, more posterior cortical areas, such as the parietal and the primary motor ones, oscillate in a lower frequency range (low beta range) compared to premotor and prefrontal cortices (high beta/gamma range). On the contrary, in comparison to healthy subjects, schizophrenic patients showed reduced natural frequency with significant lower values for the primary motor cortex and highly significant lower values for the premotor and the prefrontal cortex (Fig. 15.4). These findings confirmed the impairment of the oscillatory

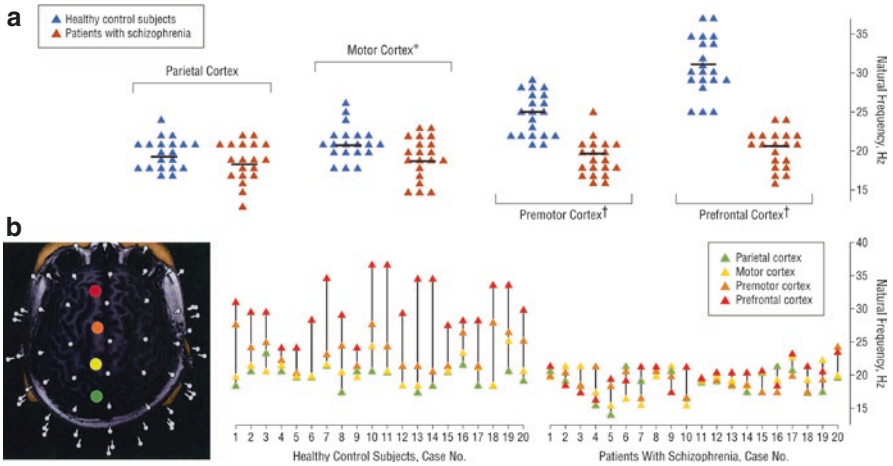

Fig. 15.4 The natural frequency of TEP oscillations is a sensitive parameter for discriminating patients with schizophrenia and healthy control subjects. In panel **a**, the individual natural frequency values of healthy control subjects and patients with schizophrenia are plotted for 4 cortical areas. Horizontal lines indicate mean natural frequency values of each group for each cortical area ($*P < 0.05$; $\dagger P < 0.001$). Panel **b** shows the natural frequency values of targeted parietal, motor, premotor and prefrontal cortical areas (red, orange, yellow, green dots on the 3D reconstruction of the cortical surface), for each study participant. (Modified from [59])

properties of the frontal thalamocortical circuits, which had been already suggested by the same research group in a previous TMS-EEG study [60] and it has been recently reproduced in patients with acute, first-episode schizophrenia [67]. Moreover, the study suggested a pathophysiological link between oscillatory deficits in the frontal lobe and clinical features of schizophrenia. Indeed, it has been observed that the prefrontal natural frequency values in patients with schizophrenia are negatively correlated with positive symptoms and that the strongest correlation was with delusion Positive and Negative Syndrome Scale (PANSS) subscores. A further TMS-EEG study conducted in psychiatric patients not only confirmed the reduction of natural frequency in schizophrenia, but also observed a similar deficit in bipolar disorder and MDD [68]. Overall, these results suggest that abnormal oscillations could be a common feature of different psychiatric disorders. Most importantly, they strengthen the hypothesis that dysfunctions in the generation of neural oscillations play a key role in the pathophysiology of major psychiatric disorders [8, 69, 70].

15.4 Future Directions for TMS-EEG in Psychiatric Research

TMS-EEG offers the possibility to directly and non-invasively measure cortical excitability and oscillatory properties, which are often altered in major psychiatric disorders. In this context, the analysis of TEPs has revealed a specific decrease or altered excitability of frontal cortical areas in MDD and schizophrenic patients compared to healthy controls. Moreover, measuring TEPs allowed to keep track of plastic modifications of the cortical circuits in MDD

patients due to invasive or non-invasive treatments, such as ECT, sleep deprivation and light therapy. Most importantly, the assessment of the intrinsic oscillatory properties of corticothalamic modules by means of TMS-EEG, i.e. natural frequency, showed that frontal circuits in major psychiatric disorders are characterized by abnormal intrinsic oscillations in comparison with healthy controls.

The few examples reported above suggest that TMS-EEG may represent a useful tool to explore the electrophysiological properties of cortical circuits in major psychiatric disorders. In this perspective, future studies may consider and further develop at least two interesting applications. First, as direct and non-invasive measures of cortical excitability, TEPs could be systematically used to assess and titrate the cortical effects of different stimulation protocols toward an individualized approach. Second, the study of TMS-evoked oscillations should be extended to other clinical populations, such as first-episode, drug-naïve patients as well as to siblings to define novel early markers of schizophrenia and to shed light on its electrophysiological underpinnings.

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