Chapter 5
Accessing Cortical Connectivity Using TMS: EEG Co-registration

TMS and Connectivity

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Abstract The combination of brain stimulation by transcranial magnetic stimulation (TMS) with simultaneous electroencephalographic (EEG) recording has the potential to be of great value for understanding the cortico-cortical connections within brain networks and how they are linked to cognitive or motor functions. It can reveal how connectivity varies as a function of neuronal state, differing between individuals and patient groups. In this chapter, we will first provide an historical overview on the development of the TMS-EEG co-registration methodology and highlight the technical challenges that need to be faced for its application. We will then discuss the wide range of possible TMS-EEG co-registration techniques and what new information may be gained on the dynamics of brain functions, hierarchical organization, and cortical connectivity, as well as on the action of TMS action per se. An advance in the understanding of these issues is timely and promises to have a substantial impact on many areas of clinical and basic neuroscience.

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R. Chen and J. C. Rothwell (eds.), *Cortical Connectivity*,
DOI: 10.1007/978-3-642-32767-4_5, © Springer-Verlag Berlin Heidelberg 2012

5.1 Introduction

Our knowledge on how different areas of the brain interact with each other and how these interactions change while subjects perform different tasks, or learn new skills, is mainly based on correlations rather than on precise cause-effect relationships. Several neuroimaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), allow to demonstrate associations between a given cognitive state and the measured patterns of brain activity. Nevertheless, the activation of an area, or a network, during a task is not sufficient to conclude that the activated areas are crucial to the involved function. Rather, it is necessary to demonstrate that the manipulation of activity in these same areas leads to changes in task performance (Bailey et al. 2001).

Transcranial brain stimulation allows for exactly this. Available techniques include transcranial magnetic stimulation (TMS) (Wassermann et al. 2008) and transcranial electrical stimulation (tES) (Nitsche et al. 2008). These techniques have gained popularity as mapping tools for studying perceptual, motor, and cognitive functions in the human brain due to their unique potential to investigate the state of targeted brain areas and/or their causal involvement in a specific function. They allow for manipulation of activity in areas of the superficial brain as an independent variable (Sack and Linden 2003) and because of this advantage, their fields of application are ever growing (Fregni and Pascual-Leone 2007; Hummel and Cohen 2006; Miniussi et al. 2008, 2010; Miniussi and Rossini 2012; Ridding and Rothwell 2007; Walsh and Cowey 2000).

Moreover, thanks to the implementation of new paradigms and new techniques for co-registering brain activity during stimulation, i.e., with EEG and fMRI, transcranial brain stimulation allows the study of functional connectivity within brain networks. Indeed, transcranial brain stimulation not only activates the targeted brain area but also areas that are anatomically and functionally connected to the target site, and thereby alters their interactions, which can transiently influence behavior.

Traditionally, TMS effects have been quantified with two different outcome measures: peripheral indices and behavioral performance. The first measure is limited to studies performed on motor areas. It is based on the fact that TMS, when delivered over the primary motor cortex with adequate intensity, activates the corticospinal tract resulting in a muscle twitch in the target muscle, named motor evoked potential (MEP). TMS effects are inferred from changes in the amplitude of these MEPs, or other features of the peripheral response, such as motor threshold, duration of silent period or spinal reflexes (Quartarone et al. 2005; Valero-Cabre and Pascual-Leone 2005) (for a discussion of the potentials of these application, see Chaps. 2, 9 and 10). The second traditional approach consists of evaluating the impact of TMS on the participant's performance in a specific task (Hilgetag et al. 2001; Pascual-Leone et al. 1994; Ruzzoli et al. 2010; Sandrini et al. 2010; Thut et al. 2005; Valero-Cabre et al. 2006) while the area considered to be engaged in the task is stimulated either directly or indirectly (by TMS over a connected site).

These two approaches of dealing with TMS-induced effects have provided an impressive amount of data, but are limited in that they do not reveal how TMS affects the stimulated area and its functioning within the whole neural network. In particular, MEPs are the result of complex events and necessarily depend on the state of different elements along the corticospinal pathway. While the “behavioural” approach has the limitation of inferring cortical effects of TMS from an indirect measure, usually reaction times or accuracy. Therefore, purely behavioral TMS studies may not reveal whether the effects primarily arise from interference with the site of stimulation, or may additionally involve interconnected brain regions.

Given these limitations, it has been advocated that alternative approaches in the use of TMS should be considered to study brain functioning and network connectivity. To this end, TMS has been combined with neuroimaging techniques such as fMRI and PET, as well as with EEG. This assists the interpretation of TMS impact upon the brain both in healthy humans and patients by providing objective and direct measurements of brain activity. This multimodal imaging approach has several advantages (Siebner et al. 2009; see also Chap. 4). First, it permits assessment of the local impact of TMS on neural processing by means of objective measures of cortical reactivity, i.e., over the directly targeted area. Second, it provides an assessment of remote effects of TMS, i.e., on neural processing in distal brain regions. Crucially, the local activation caused by the magnetic pulse is expected to spread to connected areas, which can be traced by simultaneous fMRI, PET, or multichannel EEG recording. When applied in an experimental context in which the cognitive state of the subject or the physiological state of the brain are modulated, this approach allows direct demonstration of which areas are functionally linked during a task, or how a given state shapes cortical connectivity.

Besides being a tool for evaluating cortical reactivity and connectivity, TMS can also be used to modulate brain functions in humans. Using multimodal imaging, it becomes then possible to directly monitor in vivo the neuronal consequences and eventually associated behavioral changes of stimulating an area of the cortex. Therefore, the multimodal imaging approach, such as the combination of TMS with EEG, overcomes some of the limitations of single techniques. It supplements the information provided by correlational analyses (e.g., on task-related EEG changes) with a technique that can establish a causal link between brain activity and behavior, and allows to evaluate these causal effects in the entire brain.

It is feasible to combine TMS with PET, fMRI, and EEG. Which combination to select depends on the specific aims of the study. Each combination focuses on different aspects of TMS-induced changes in brain activity. TMS-PET and TMS-fMRI co-registration are of interest because these techniques can in principle reveal the spatial profiles of transcranial brain stimulation effects with high spatial resolution, including in subcortical structures ipsilateral and contralateral to the stimulation site (Siebner et al. 2009). Nevertheless, these techniques are based on changes in blood flow and oxygenation, which typically occur a few seconds after changes in neuronal activity. They therefore have a reduced temporal resolution and can only detect modulations arising a few seconds (fMRI) or even minutes (PET) post-stimulus. Given that TMS-induced brain activity occurs within a few hundreds of milliseconds after the TMS impulse, these techniques do not address the high temporal resolution window during which profound and functionally relevant TMS-induced neural events are thought to take place (Bonato et al. 2006; Komssi and Kahkonen 2006).

When the timing of the TMS-induced cortical activity is relevant, EEG provides a suitable method to complement TMS. In addition and possibly as a result of this high temporal resolution, EEG seems particularly sensitive in revealing the neuronal effects of TMS. For example, BOLD MRI does not detect any changes in brain activity when TMS is delivered at subthreshold intensities, i.e., at about 80 % of motor threshold (Bohning et al. 1999). In contrast, it has been shown that several TMS-evoked responses can be recorded by EEG when TMS is administered at 40 % of resting motor threshold (Komssi et al. 2007). Additionally, thanks to computer technology that enabled the development of portable EEG recording, TMS-EEG is also a promising neurophysiological technique that is feasible at the patients' bedside for diagnostics purposes and may have clinical utility. However, EEG has a poor spatial resolution and the cortical localization of the TMS effects can only be inferred from source localization algorithms.

5.2 Early TMS-EEG Studies

The first attempt of TMS-EEG co-registration was reported in 1989 by Cracco and collaborators (1989) who investigated inter-hemispheric transcallosal conduction time. Activity was recorded from an electrode placed over the left premotor cortex (between F3 and C3, corresponding to the posterior part of the middle frontal gyrus, Brodmann area 6), while stimulating the homologous contralateral site. A positive deflection was reported contralateral to stimulation peaking at 9–12 ms after the TMS pulse (Cracco et al. 1989).

Subsequently, only one paper reported the use of TMS-EEG (Amassian et al. 1992) until 1997, when a new generation of amplifiers was introduced (Ilmoniemi et al. 1997; Virtanen et al. 1999). The reason why this approach was not applied was related to technical limitations and saturation of the EEG recording system caused by the strong electromagnetic pulse. Ilmoniemi et al. (1997) reported for the first time TMS-induced activity recorded with multichannel EEG (60 recording electrodes). Their TMS-EEG co-registration system was equipped with a sample-and-hold circuit that could block the EEG amplifier signal for a few micro- to milliseconds for the duration of the TMS discharge (for similar approach see also Iramina and Maeno 2003; Taylor et al. 2007b; Virtanen et al. 1999). This avoids saturation of the recording amplifiers by the electromagnetic pulse, allowing the recording of EEG activity shortly after TMS delivery.

Since then, several groups have applied this methodology (see e.g., Komssi and Kahkonen 2006). Other amplifiers that are not saturating but allow continuous data recording throughout TMS have also been tested and successfully used (e.g., Bonato et al. 2006; Fuggetta et al. 2006; Ives et al. 2006; Taylor et al. 2010;

Veniero et al. 2010). This has led to reports of several possible applications (Komssi and Kahkonen 2006; Siebner et al. 2009; Taylor et al. 2008; Thut and Miniussi 2009). Nowadays, it is therefore possible to run continuous EEG recordings during TMS stimulation. Nevertheless, this new technology still poses some problems related to the very high-energy component of the TMS pulse that we will review in the following section.

5.3 The Basics of EEG-TMS Studies

The TMS pulse has a very high-energy component and it most likely induces charges in electrodes, leads, amplifiers, and skin that last longer than the TMS pulse. Therefore, at least part of the initial large response recorded after TMS stimulation is due to non-cortical currents induced by the magnetic field.

In several papers, it was reported that it is not possible to record a clear EEG signal in the first 30–300 ms after TMS (Bender et al. 2005; Morbidi et al. 2007; Taylor et al. 2008; Thut et al. 2003). Several reasons can account for the long-lasting TMS artifact. The main reason may be that electrodes and skin have magnetic properties, and may therefore be affected by the TMS pulse and generate non-cortical signals in the recording. EEG is traditionally performed with electrodes made of tin, silver, silver-chloride, or gold, with a fairly large and ring-shaped surface. This standard electrodes permit eddy currents to be generated during TMS, which can cause heating or even movement of the electrodes. In terms of safety, this poses a risk of scalp burns under the electrode (Pascual-Leone et al. 1990, 1993; Rossi et al. 2009; Roth et al. 1992; Veniero et al. 2009). With regard to signal quality, heating and movement can induce electrical artifacts and reduce the signal to noise ratio. Eddy currents and therefore overheating of the electrodes located in the vicinity of the stimulating coil may be minimized by cutting out a section of the ring metal electrodes to create a radial notch (Roth et al. 1992). Plastic electrodes have also been used (Ives et al. 2006) but with a conductive-silver epoxy coat. Moreover, it has been shown that by using TMS-compatible pellet electrodes, it is possible to obtain the same result without cutting the electrodes (Virtanen et al. 1999, 2009).

To resolve this artifact issue, several procedures have been proposed. Subtraction approaches are based on creating templates of the TMS-induced artifact by collecting data while TMS is applied on a phantom (Bender et al. 2005) or in a condition that does not involve a task (Thut et al. 2003). To isolate brain signals from the TMS-induced artifacts, the template is then subtracted from data collected in the experimental condition, in which TMS is applied during a task. Moreover, if in some electrodes the signal is irremediably contaminated by the TMS artifact, these electrodes can be excluded from further analyses (Komssi et al. 2004). Other, alternative solutions to remove TMS-induced artifacts are based on filtering methods (Morbidi et al. 2007), principal component analysis (Litvak et al. 2007), and independent component analysis (Hamidi et al. 2010).

To establish optimal conditions for recording EEG during TMS, Veniero et al. (2009) studied artifact-inductions while systematically manipulating various technical parameters (TMS pulse configurations, TMS coils, EEG settings, electrode impedance, wire orientation). Note that the parameter space was explored for a TMS-compatible EEG system that allows continuous recordings. Information on absolute artifact-duration may only apply for this particular system, but relative differences across parameters should generalize to other systems. To better characterize the TMS artifact and to exclude any physiological response, recordings were performed with TMS of a phantom 'head' and then compared to the recordings obtained from knee stimulation and cortical stimulation. EEG signal was acquired at 5,000 Hz and band-passed at 0.01–1,000 Hz. Different types of TMS pulse configurations and stimulators (monophasic, biphasic with four boosters, and biphasic with single power supply module), different TMS coils (four figure-of-eight coils, i.e., standard 50–70 mm, custom 25–70 mm), several TMS intensities (ranging from 10 to 100 % of the stimulator output), and frequencies of stimulation (single pulse, 5 Hz and 20 Hz) were compared. The main results indicated that, regardless of the above-cited parameters, TMS-induced artifact always lasted about 5–6 ms, as can been seen in Fig. 5.1. One critical variable influencing artifact-duration was the choice of the EEG acquisition settings. Lower sampling rate and filters caused rippling of the signal, and an increase in the duration of the TMS-induced artifact, preventing the sampling of information shortly after the pulse. Moreover, the impendence values of EEG electrodes also played an important role in artifact contamination, as it was found that for high impedances (about 20 kΩ), EEG signal recovery time was slower (15–20 ms) and artifact amplitude was higher (>two times) than for lower impedances (0–3 kΩ) (see also Julkunen et al. 2008b).

Besides the above described TMS-artifact, EEG signals can also be contaminated several tens of milliseconds after the TMS pulse with a coil-recharge-artifact that is present with biphasic but not monophasic stimulators (Veniero et al. 2009). Finally, to keep the artifact minimal, Veniero et al. (2009), found that the wires should be arranged in an orientation away from the coil or coil cable, regardless of where stimulation takes place on the head. The reorientation of the wires before stimulation can therefore help to record clearer signals (see also Sekiguchi et al. 2011).

Apart from optimizing recording parameters, it is important to consider that TMS can also induce nonspecific or indirect brain responses, which may influence the EEG recording (Komssi and Kahkonen 2006; Miniussi and Thut 2010; Taylor et al. 2008). These nonspecific, task unrelated contaminations consist of (i) auditory responses due to the coil click; (ii) somatosensory responses mostly due to trigeminal afferents or afferent responses after motor cortex stimulation; and (iii) muscular responses because of eye blinks and startle induced by the coil click, and peripheral muscular contractions due to peripheral stimulation. Also, general arousal due to TMS or auditory intersensory facilitation induced by the coil click might be present. All these effects should be eliminated or masked whenever possible (e.g., Massimini et al. 2005). In instances where this is not possible, these artifacts should, as part of the experimental design, be reproduced in separate conditions (i.e., via control stimulation at appropriate sites), and their effects should be taken into account during data analysis and interpretation.

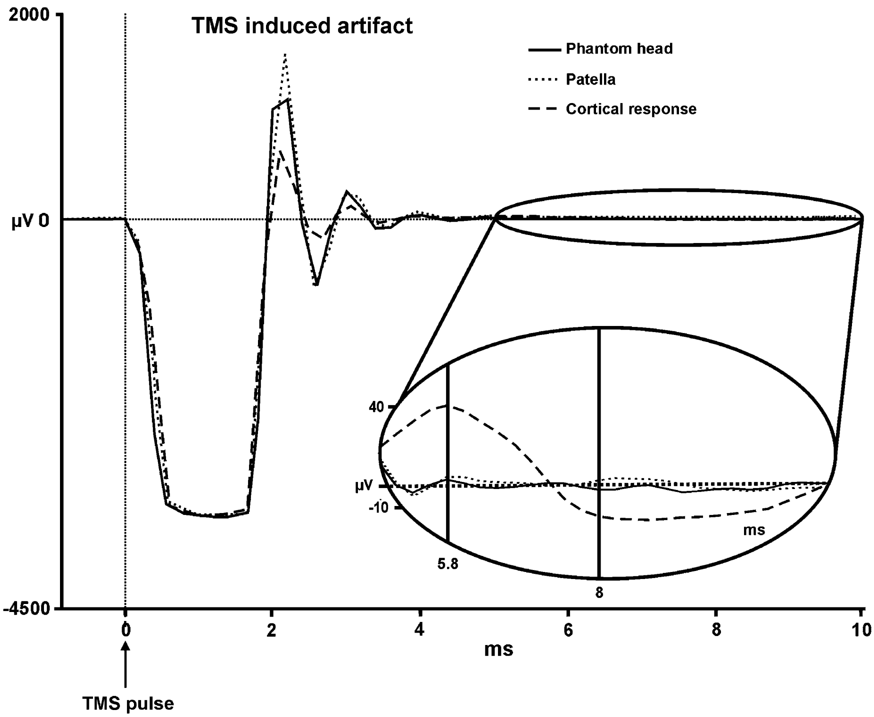

Fig. 5.1 TMS-induced artifact as recorded from three different models: the phantom head, patella and cortical stimulation. The stimulus intensity was set at 50 and 40 % of maximum stimulator output (MSO) as well as at individual resting motor threshold (57 % of MSO), respectively. Signal from the phantom and patella was recorded from the electrode beneath the coil, while the cortical response was acquired from Cz. The EEG recorded from 5 to 10 ms is magnified for clear visualization (from Veniero et al. 2009)

5.4 Instruction of Use

In the last few years, the TMS-EEG co-registration has been applied to study the brain from different perspectives. These will be described below along three main lines of applications (recently proposed by Miniussi and Thut 2010), the inductive, interactive, or rhythmic TMS-EEG approach.

5.4.1 Inductive Approach: Connectivity and TMS-Evoked Potentials

In the inductive approach, which also represents the first EEG-TMS application used (Ilmoniemi et al. 1997), TMS-evoked potentials (TEPs) are measured from the scalp while subjects are in a resting state, i.e., they are not performing any task (Bonato et al. 2006; Esser et al. 2006; Ilmoniemi et al. 1997; Iramina and Maeno

2003). The rationale for using an inductive approach is to probe the state of the cortex and to evaluate cortical excitability and connectivity. Cortical excitability is probed by studying the reactivity of the target area (usually in response to a single TMS pulse), the amplitude of the TEPs being dependent on the stimulation intensity, thus reflecting the reactivity of the stimulated cortex (Komssi et al. 2004, 2007). In analogy to MEPs, TEPs represent quantifiable markers of cortical excitability. However, TEPs have three crucial advantages over MEPs. First, TEPs are a direct measure of cortical reactivity, whereas, MEPs are a peripheral index that can be influenced by other factors. Second, TEPs allow investigation of the areas considered behaviorally silent, i.e., areas where stimulation does not yield directly observable behavioral effects. Third, TEPs provide a method to investigate brain connectivity (Komssi et al. 2002; Massimini et al. 2005) in normal participants, and in neurological and psychiatric disorders. Indeed, when a cortical region is stimulated, the spreading of the induced activity can be traced by means of the distribution of the EEG signals over the scalp, or their cortical source reconstruction.

TEP-components and TEP-topographies are one of the simplest ways to evaluate cortico-cortical connectivity with TMS–EEG co-registration. For example, using the same approach that has been used to evaluate interhemispheric transfer of information (Ipata et al., 1997), it should be possible to subtract the latency of TEP-components evoked by TMS of a given area from the latency of the same components evoked by the stimulation of the contralateral homologous area. This will give the possibility to estimate the interhemispheric transfer time between two areas that are considered to be directly connected. Nevertheless, we would expect that activity spreads not only between homologous areas. Therefore, to be able to track signal spreading across the cerebral cortex, more complex analyses must be carried out, such as the use of EEG source localization algorithms.

This approach was implemented by Ilmoniemi et al. (1997) (but see also Komssi et al. 2002) who computed activation maps from TEPs using minimum-norm estimates. The analysis was focused on the waveform, latency, and cortical distribution of TEPs. Ilmoniemi et al. (1997) showed that TMS of motor cortex induced a direct activation of the stimulated motor area (at latencies of 3 and 10 ms), followed by a spreading of neuronal activation to ipsilateral premotor areas and then to the contralateral hemisphere (at 24 ms).

Precise sources localization of TEP-components was performed by Litvak et al. (2007). Using a multiple source dipole model, they found an ipsilateral activation of the stimulated motor cortex, of the cingulate gyrus/supplementary motor cortex as well as of the cerebellum. Litvak et al. (2007) provided a direct demonstration that it is possible to implement the spatio-temporal decomposition approach to identify singular nodes of the probed network.

A few studies have employed the inductive approach to evaluate altered connectivity in diseases such as Alzheimer disease (AD) (Julkunen et al. 2008a) and as a tool for diagnostics and early identification of mild cognitive impairment (MCI). Julkunen et al. (2008a) showed that stimulation of the motor cortex in AD patients was associated with prominent changes in functional cortical connectivity. Namely, they found a significant decrease in the TMS-induced activity over several brain areas in AD patients compared with healthy controls, suggesting a dysfunction of a large-scale sensorimotor network.

Moreover, the inductive approach has been successfully applied in numerous studies to investigate cortical connectivity as a function of different physiological states of the subject. For example, Kahkonen et al. (2001) used this approach to evaluate how cortical responses can change based on the "modulation" of the physiological state with ethanol consumption. Cortical distribution of TEPs was evaluated in a group of subjects before and after ethanol consumption. Results showed mainly prefrontal differences in TEP maps before as compared to after ethanol ingestion. The data revealed that ethanol consumption can change the functional connectivity between prefrontal and motor cortices providing direct evidence that the modulation of cortical connectivity can depend on the physiological state of the nervous system.

Zanon et al. (2010) investigated the spreading of activity from the left parietal cortex to prefrontal regions in healthy volunteers. Their findings suggest that the parietal regions are connected with the contra-lateral prefrontal regions and that this connection was activated in a time range of 100–170 ms after the TMS. Moreover, they revealed a connection between parietal regions and the ipsilateral temporo-occipital cortex, showing that it was possible to track the presence of specific contra- as well as ipsilateral cortical connections. However, volunteers were asked to stay in a rest position with closed eyes. It is therefore difficult to draw a specific conclusion about functional connectivity among parietal cortex and other regions in other physiological states.

In a similar study on connectivity, Massimini and colleagues (Ferrarelli et al. 2010; Massimini et al. 2005) stimulated the premotor cortex of subjects while they were in different states (i.e., awake or sleeping) in order to evaluate how state influences connectivity. In both conditions, the local TEPs were similar, whereas the remote responses differed dramatically. During wakefulness, TMS induced activity spread within and between hemispheres, whereas during sleep, activity remained confined to regions surrounding the stimulated area.

The importance of these studies is that they illustrate how effective connectivity (i.e., the functional interactions between distinct elements within a nervous system) changes depending on the state of the subject. This introduces the concept that cortical connections of a stimulated area cannot be considered to be independent from its functional status (Ferrarelli et al. 2010; Massimini et al. 2005). These aspects suggest that the functional effects induced in one area could be co-opted into different functions depending on the state of activation (state dependency) or which of its interconnected networks were activated (e.g., Harris et al. 2008; Selimbeyoglu and Parvizi 2010; Silvanto et al. 2005).

5.4.2 *Interactive Approach: Cortical Connectivity While the Subject is Performing a Task*

The interactive approach refers to EEG-TMS experiments in which subjects are asked to perform a task and TMS is used to interact with a specific brain region thought to be involved in a given function. In this case, EEG is used to reveal the network affected by TMS (which could involve the targeted area, any interconnected region, or both), to measure the timing of the induced activity changes and how the TMS-induced perturbation correlates with performance (Miniussi and Thut 2010; Taylor et al. 2008). The rationale of this approach is to gain insights into how neural areas interact during task preparation and execution (Nikulin et al. 2003), allowing not only to study the causal role of specific brain areas in behavior, but also, when and how one area affects the activity in other areas (Taylor et al. 2007a, b).

When combined with EEG recordings, TMS offers the opportunity to modify and assess in real time the neural dynamics of widely distributed networks engaged in performing different tasks or learning new skills. EEG allows identifying the local and global brain activities associated with behavioral manifestations of task execution or learning, and TMS can be used to modify these activities to link neuronal with behavioral changes.

As reported in the previous section, active interactions between distant cortical areas have been shown to vary with the functional state of the brain (Massimini et al. 2005). In the motor system, an increase in MEP-amplitude can be achieved by voluntary contraction of the target muscle (Rothwell et al. 1987). Similarly, cortical connections have been shown to be 'modulated' by the system state. Ferbert et al. (1992) showed that the excitability of the transcallosal connections between motor cortices changed depending on whether the subject contracted one or both hands. These findings suggest that TMS effects are sensitive to changes in the cortical state and open the intriguing possibility that administration of TMS-EEG while a subject performs a behavioral task may permit targeting and highlighting specific circuitries.

The work by Morishima et al. (2009) followed exactly this logic. They used TMS as a probe to evaluate the neural impulse transmission from the prefrontal cortex to posterior regions. It is believed that an attentional network exists where top-down signals from the prefrontal cortex modulate the neural processing in the posterior cortices according to behavioral goals (Corbetta and Shulman 2002; Desimone and Duncan 1995). Morishima et al. (2009) hypothesized that stimulation of prefrontal areas of the attentional network would induce a current spread toward the anatomically connected posterior regions, and that the direction and the amount of the current spread could be modulated depending on the functional status of the neural network, the latter set by the task performed by the subjects. During cued attention to visual feature, TMS of the frontal eye field induced activity in different posterior visual areas depending on the nature of the visual feature (Morishima et al. 2009). Moreover, the TMS-EEG approach of effective connectivity used by Morishima et al. (2009) also provided information about the interplay between the prefrontal and posterior areas. TMS effects occurred 20–40 ms after the pulse, suggesting that it was not due to rerouting via other areas, but that there was a direct cortico-cortical signal transmission from frontal to posterior regions.

This illustrates the importance of the interactive approach in the application of the TMS-EEG co-registration. The approach yields real-time measures of whole-brain activity changes while subjects are performing a task and specific areas of the network are concurrently stimulated (real connectivity).

5.4.3 Rhythmic Approach: Connectivity and EEG Frequencies

Combining EEG with TMS can also be used to evaluate changes to brain oscillations in specific frequency bands in a specific area or in the entire brain.

Electrical brain activity consists of distinct patterns of oscillations associated with different perceptual, motor, and cognitive processes (Buzsàki 2006). TMS is expected to change such oscillatory patterns in the directly stimulated cortical area as well as in distant areas belonging to the same neural network. In this respect, the rhythmic approach refers to the possibility of investigating how TMS interacts with oscillatory brain activity (Thut and Miniussi 2009).

A few studies have evaluated the after-effects of repetitive TMS (rTMS) over the motor cortices (Oliviero et al. 2003; Strens et al. 2002). Stimulation of the left motor area at low TMS frequency induced an increase in ipsilateral coherence and in interhemispheric coherence between motor areas in the alpha band (Strens et al. 2002), whereas stimulation at high TMS frequency induced opposite results (Oliviero et al. 2003). These changes may be explained by differential effects on neuronal circuitry linked to inhibitory versus facilitatory processes depending on the stimulation frequency (low- vs. high-frequency rTMS). This would be in line with the idea that low frequency ($\leq$1 Hz) stimulation generally results in inhibition, whereas high frequency ($\geq$5 Hz) stimulation mainly results in excitatory changes in the stimulated area (Chen et al. 1997; Maeda et al. 2000). Nevertheless, it has also been shown that stimulating at different frequencies (1 vs. 20 Hz) over the resting motor cortex (Brignani et al. 2008; Veniero et al. 2011) can induce a power increase in the alpha band, as illustrated in Fig. 5.2. Considering the state of the cortex, these data suggest that alpha generation may represent an intrinsic induced response to TMS targeting the human resting motor cortex.

Low-frequency TMS to the motor or premotor cortex has been shown to affect alpha-activity over ipsilateral motor and to a lesser extent, over contralateral homologous sites (Chen et al. 2003), congruent with enhanced functional interconnectivity of these regions during a motor task (but see also Jing and Takigawa 2000 for high frequency stimulation of the prefrontal cortex). Plewnia et al. (2008) using a new approach evaluated EEG coherence after synchronous bifocal rTMS. Based on the concept of assembly through associative stimulation (Hebbian learning), they hypothesized that by applying synchronous bifocal rTMS over two areas, it might be possible to induce a topographically selective enhancement of interregional coherence. Trains of high-frequency rTMS were applied to the left primary motor cortex and the visual cortex simultaneously. They found that this approach induced a selective increase of interregional coupling in the alpha and lower beta band on the

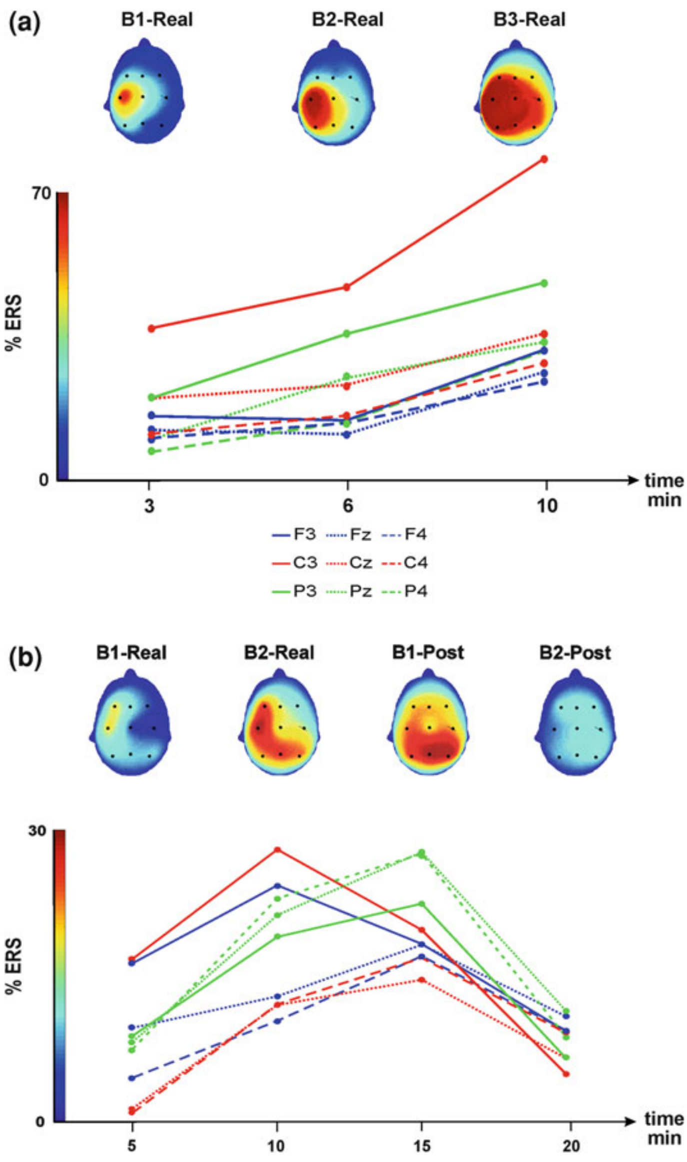

Fig. 5.2 Scalp distribution maps of the event-related power modulations induced by 1 Hz (Panel a) and 20 Hz (Panel b) rTMS for the alpha frequency band using the sham TMS as reference. 1 Hz rTMS data are represented separately for the three successive stimulation blocks (B1, B2, B3 Real) during TMS (Panel A). 20 Hz rTMS data are represented for two successive stimulation blocks (B1, B2 Real) during TMS and two stimulation blocks (B1, B2 Post) after the end of TMS. Voltage is color coded according to the color bar on the left, red color represents maximum relative synchronization. On the x-axis the time of recording in minutes is reported. In the lower part, data are shown for each recording electrode and stimulation block (adapted from Brignani et al. 2008; Veniero et al. 2011)

stimulated sites that lasted up to ten minutes after stimulation (see also Brignani et al. 2008; Veniero et al. 2011). The authors proposed that according to Hebb's rule, enhancement of synaptic efficacy by bifocal simultaneous stimulation may reinforce the connections among cortical areas, as reflected by an increase of oscillatory coupling. It has also been shown that when TMS is tuned to the frequency of the underlying generator (frequency tuned rhythmic TMS), this can entrain on-going brain oscillations in a controlled manner (Thut et al. 2011a) with specific perceptual or behavioral consequences (e.g., reviewed in Thut et al. 2011b). In analogy to Plewnia et al. (2008), it was therefore concluded that rhythmic TMS can be used to generate natural oscillatory signatures.

The rhythmic approach has also been used in a study by Schutter and van Honk (2006) to demonstrate the functional link between cerebellum and frontal areas. Prefrontal and frontal theta activity was observed 200 ms after single-pulse TMS over the cerebellum, therefore, demonstrating a functional connection from the cerebellum to the prefrontal cortex. These results were in line with early animal studies showing cerebellar connectivity to brain structures involved in cognitive and emotional functions (such as the frontal cortices), as well as with studies showing that chronic stimulation of the cerebellum through implanted electrodes normalized the behavior of emotionally dysregulated patients (Heath 1977).

Using a similar rationale, Capotosto et al. (2009) applied TMS over areas known to be involved in the control of visual spatial attention, namely frontal eye-field (FEF) and intraparietal sulcus (IPS), and investigated remote changes in oscillatory activity. Both FEF and IPS stimulation led to a change of the remote regulation of alpha-activity contralateral to attended versus unattended space. This shows that manipulation of activity of an area implied in top-down control leads to a change in oscillations of a downstream network area implied in stimulus processing.

Therefore, this approach offers the possibility to elucidate the relationship between specific oscillatory activity of a network, the interplay between areas and relation to behavior. Moreover, the rhythmic approach can be used to actively generate specific oscillatory signatures and thereby test the functional role of brain rhythms in affective and cognitive functions (for a review see Thut and Miniussi 2009) in connected areas.

5.5 Conclusions

TMS-EEG co-registration offers the unique advantage to simultaneously manipulate and evaluate brain activity and thereby provides valuable information on cortical reactivity and connectivity. The reviewed findings suggest that these measures are highly sensitive to changes in the cortical state, and can be employed to evaluate changes in the connectivity of a given area as a function of different physiological and pathological conditions. Because the brain operates through flexible and interactive distributed networks, we would expect that the modification of a node of the network affects the entire network. If brain stimulation is applied when the system is in a given functional state, it will bring to evidence the cortico-cortical (or subcortical) network that is effectively connected to the target area at time of TMS, and eventually how that network can be modified by specific tasks, different physiological or pathological states, and pharmacological or behavioral (rehabilitative) treatment approaches.

The significance of concurrent EEG and TMS arises from the possibility to record neuronal responses to the magnetic pulse with a millisecond time scale. This proofs to be a very sensitive method for recording the impact of TMS on the brain and neuronal processes. All in all, this method provides a new way of mapping effective cortical connectivity.

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