Chapter 8

Transcranial Magnetic Stimulation and Neuroimaging Coregistration

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1. Introduction

The development of neuroimaging techniques is one of the most impressive advancements in neuroscience. The main reason for the widespread use of these instruments lies in their capacity to provide an accurate description of neural activity during a cognitive process or during rest. This important advancement is related to the possibility to selectively detect changes of neuronal activity in space and time by means of different biological markers. Specifically, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and near-infrared spectroscopy (NIRS) use metabolic markers of ongoing neuronal activity to provide an accurate description of the activation of specific brain areas with high spatial resolution. Similarly, electroencephalography (EEG) is able to detect electric markers of neuronal activity, providing an accurate description of brain activation with high temporal resolution. The application of these techniques during a cognitive task allows important inferences regarding the relation between the detected neural activity, the cognitive process involved in an ongoing task, and behaviour: this is known as a *"correlational approach"*.

Besides the fascinating perspective that neuroimaging techniques offer, their correlational nature also represents one of the main limitations since it does not permit to establish causal inferences on brain-cognition-behaviour relations. The development of tools such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)[1] have compensated for this limit. These instruments, in fact, are able to actively interfere with the ongoing brain activation, permitting to establish a directional (i.e., causal) link between a

[1] The tDCS technique will not be covered in this chapter. Its use with concurrent neuroimaging is very recent since only a few studies so far have investigated this possibility (see [10], for a review).

brain area and a cognitive process. Transcranial magnetic stimulation generates a brief and strong current through a stimulation coil which, in turn, induces a perpendicular, high time-varying magnetic field that penetrates the cranium unimpeded and painlessly [1]. The changing magnetic field induces a transitory electric current that causes depolarisation of a focal population of neurons. Traditionally, this feature has been used to provide a non-invasive measure for neurophysiologic investigation of the central and peripheral nervous systems. Only in the last twenty years the TMS capacity of inducing a transient and focal depolarisation has been utilised in cognitive neuroscience research to allow inferences regarding the role of cerebral areas during the execution of cognitive tasks [2].

However, despite the widespread use of TMS, its exact mechanism of action and interaction with ongoing neural activity is still unclear. In fact, some studies have reported contrasting effects of the same TMS protocol both in cognitive performance, whose execution can be facilitated or inhibited (e.g., [3,4]) and in therapeutic protocols of repetitive TMS (see section 1.2), which can generate the opposite effect in cortical excitability modulation though keeping the same parameters of stimulation [5]. Recent studies have stressed the importance of clarifying the physiological mechanism of TMS [6] and the need to disambiguate its effects on the physiological and behavioural domains [7]. A univocal explanation of the contrasting outcomes after TMS application has not been provided yet, probably because of its complex and variable interaction with brain activity, which can result in the aforementioned unpredictable outcomes. Depolarisation induced by TMS might in turn activate both local neurons under the coil and neurons that project axons far away from the site of stimulation [8]. Moreover, the TMS pulse might activate a mix of neurons, both excitatory and inhibitory. This could be another factor that can lead to contrasting effects [9]. To this end, neuroimaging techniques potentially offer a promising contribution through the description of brain activity evoked by TMS. Recently, many studies have combined TMS with neuroimaging techniques in a coregistration approach and currently this methodology represents a promising answer to some of the unsolved questions regarding the brain-cognition-behaviour relationship.

In this chapter the combined use of TMS and neuroimaging will be widely discussed with particular regard to its advantages as well as its methodological and technical aspects. In the first section the novelty value of TMS-neuroimaging coregistration will be covered with a discussion of how TMS can compensate for the limits of neuroimaging techniques and, vice versa, how neuroimaging could extend the results provided by TMS. In the second section common methodological aspects among the different TMS-neuroimaging coregistrations will be discussed. The third section will focus on TMS-EEG coregistration with regard to the advantages, clinical and research applications, and technical issues that greatly concern the simultaneous use of these two instruments. Finally, the last section of the chapter provides a review of coregistration studies with the other techniques (fMRI, PET, SPECT and NIRS) that will be carried out. The use of such techniques in combination with TMS is more recent than TMS-EEG coregistration. Thus, the review of these methodologies will be relatively shorter in comparison to the discussion on the more popular TMS-EEG methodology.

2. From correlation to coregistration

2.1. What can neuroimaging add to TMS?

One of the most controversial aspects of TMS lies in its complex physiological mechanism. In fact, despite the widespread use of TMS in current research, its mechanism of action is still poorly understood. The ability of TMS to interfere with brain activity is based on the principle of the electromagnetic induction of an electric field, namely Faraday's Law. According to this law the exposition of a material to a time-changing magnetic field causes the induction of an electric field. When TMS is applied to the brain, these electric currents cause a transient and non-invasive depolarisation of cell membranes and thereby neuronal activation in the stimulated area [1]. The application of TMS to the hand representation in the primary motor cortex, for example, induces a depolarisation of the neurons of the corticospinal tract, which evokes a muscle twitch in the contralateral hand. The size of the motor-evoked potential (MEP) reflects the excitability of the corticospinal system. This is one of the few "visible effects" that TMS induces when it is applied to the brain and currently most of the knowledge on the physiological mechanisms of TMS is based on the analysis of such peripheral markers. At the end of the 1980s, the TMS capacity of inducing a non-invasive, transient, and relatively focal depolarisation was used for the first time as a "disruptive" technique, whose effects were interpreted in terms of "virtual brain lesions" [11]. This term was proposed considering the TMS effect as inducing a temporary, reversible lesion in the stimulated area. The "virtual lesion" interpretation of the TMS mechanism was widespread for two main reasons: first, it was supported by early studies on cognitive processes (e.g., [12]); second, it was the most parsimonious and simple explanation of the TMS effect. With the development of neuronavigation systems (see section 4.1), the idea of TMS as a "point and shoot" methodology grew further, until several experiments showed that TMS could also result in the facilitation of cognitive performance (e.g., [4,13]). These "paradoxical" facilitation effects revealed the inadequacy of a "virtual lesion" hypothesis in explaining TMS effects, leading to a reconceptualisation of its mechanisms. Recently, new evidence from biophysical and neuroimaging studies (e.g., [14,15]) offered new insights into basic properties of TMS, leading to an interpretation of its effect in terms of a random-induced neuronal activity ([16]). This activity can be thought of as "neural noise" since is not directly associated with the activity of the stimulated area. For these reasons, its effect can result in interference or facilitation of a cognitive performance depending on the relationship between the noise (i.e., TMS-evoked activity) and the signal (i.e., target activity) [16]. Nevertheless, besides the credible contribution of these kinds of studies clear evidence of the TMS physiologic mechanisms has not yet been provided.

Neuroimaging techniques offer an important contribution to TMS mechanism comprehension through the description of the neural activation evoked by the electromagnetic pulse. For instance, electroencephalography (EEG) can detect the response of a cortical area to the TMS pulse (i.e., cerebral reactivity) based on the related electric markers of its activity, namely TMS-evoked potentials (TEPs). The analysis of TEP characteristics such as latency, amplitude, polarity, and waveform can offer an insight into the physiological state of the stimulated brain

area, allowing researchers to tackle inference with TMS mechanisms. On the other hand, techniques such as fMRI, PET, SPECT, and NIRS, which provide better spatial resolution than EEG, offer a detailed picture of responses to TMS throughout the brain. One of the most direct exemplifications of a neuroimaging contribution is the demonstration of the spread dynamics of TMS-evoked activity from the stimulated area to the connected regions. Ilmoniemi and colleagues ([17] – discussed below in section 2.2) were the first to provide direct evidence of this phenomenon. The authors mapped the ongoing activity evoked by the stimulation of the primary motor cortex and primary visual cortex in the ipsilateral and contralateral homologous regions. This evidence had a high novelty value in the field of TMS research, considering that traditionally its effects were evaluated only in regard to the stimulated area. Besides the elucidations on the general TMS mechanism, neuroimaging techniques can also provide direct evidence on the effect of a single TMS parameter. An example was provided by Käkhönen and colleagues [18]. The authors investigated reactivity variations of the prefrontal cortex and primary motor cortex across different stimulation intensity conditions. All the different contributions that each neuroimaging technique provides to TMS will be further discussed in the following sections of this chapter.

2.2. What can TMS add to neuroimaging?

The correlational nature of neuroimaging techniques does not allow any conclusion about the causal role of an activated brain region in task performance. Basing on fMRI data for example it can be demonstrated that an *X* cerebral area is activated while a *Y* cognitive process is performed. However, from a logical point of view this evidence is not sufficient to establish that if the *X* area is activated, the *Y* process is being performed [19]. This argument, which has not been legitimated by scientific logic, is known as "reverse inference" [20]. Furthermore, besides the accurate spatio-temporal information, neuroimaging instruments cannot account for most of the complex variability in neurobiological mechanism modulation. One of the main limitations of these techniques in fact is the poor information about the nature of the brain activation. Basing on PET or fMRI data for example it cannot be established whether the observed activity is excitatory or inhibitory [21]. This is a crucial aspect since the activity detected in a certain area might also reflect inhibitory activation aimed to stop or inhibit processes competing with the function of the area. Moreover, a brain area could merely be accidentally activated by a cognitive process [21]. Finally, in the presence of diffuse brain activation during a multi-componential cognitive task, functional neuroimaging cannot discriminate between the different contributions of the activated brain areas within the ongoing cognitive process [22]. These factors pose several problems in demonstrating the role of a certain area within a cognitive process. In summary, since a brain region can be considered crucial in an *"X"* cognitive process only if the modulation of its activity affects cognitive performance (i.e., facilitation/disruption of the performance), the manipulation of brain activation as a variable is a critical factor in establishing its particular causal role. This feature is provided by transcranial magnetic stimulation technique.

The active interference provided by TMS is used frequently in current neuroscience research to make causal inferences regarding the functional contribution of a stimulated brain area.

There are three main TMS protocols, and their use generally depends on the goal of the application: "single-pulse" (spTMS), "paired-pulse" (ppTMS), and "repetitive" (rTMS). Single-pulse stimulation is mostly used to transiently "interfere" with instantaneous cerebral process, providing an accurate description of the cerebral processing timing. This stimulation is commonly used in the investigation of motor and cognitive process functioning. Regarding the first, spTMS provides precise measures of corticospinal excitability, such as motor threshold (MT) and cortical silent period[2], which are common indices in TMS studies. Regarding cognitive processes, spTMS allows the study of cognitive processing in a causal way through the measurement of reaction times and the accuracy of a performance while delivering a pulse at different time intervals from the stimulus onset (e.g., [23]). The high time resolution provided by spTMS can be used to identify critical periods during which the stimulated area and its connections cover a crucial role within the ongoing process (i.e., mental chronometry – [2]).

Paired-pulse stimulation consists of two pulses and is mostly used in the study of inhibitory processes of motor and premotor cortices. This stimulation can be delivered by one or two coils located in two different areas; in the latter case, we refer to it as "twin-coil" stimulation [24]. This procedure permits the investigation of motor-associated area interactions by analysing variations in MEP amplitude evoked by a test coil placed over the primary motor cortex [24,25]. The other coil, referred to as conditioning coil, is placed over another scalp site. If the conditioning stimulus, which is given prior to the test stimulus over M1, induces a variation in the amplitude of the test MEP (i.e., facilitation or inhibition), a functional connectivity between the two sites with regard to its timing and nature (i.e., facilitatory or inhibitory) might be inferred. Pulse intensities and inter-stimulus-intervals (ISIs) also provide different effects. An ISI of a few milliseconds is generally used in the investigation of short-interval cortical inhibition processes (SICI – [26]), whereas a longer ISI (e.g., 50-200 ms) is generally used in the study of long-interval cortical inhibition processes (LICI – [27]). Different effects can be observed also by varying the intensities of the two stimuli: lower intensities and short ISI generally deliver facilitatory effects [28], whereas inhibitory effects are often observed with higher intensities [24].

Repetitive stimulation consists of a "train of pulses" delivered in a certain time frequency. In the literature, stimulation with a frequency higher than 1Hz is referred to as "high-frequency rTMS", whereas stimulation with a frequency of less than 1Hz is referred to as "low-frequency rTMS" [29]. Repetitive TMS, unlike spTMS and ppTMS, can produce an effect on the excitability of a stimulated area for a period that lasts beyond the duration of the TMS application, depending on the stimulation parameters. For this reason, it has been used frequently both in cognitive studies (e.g., [30] – discussed in section 1.3) and in clinical applications, especially regarding major depression (e.g., [31]), Parkinson's disease (e.g., [32]), and epilepsy (e.g.,[33]) it has been generally established that a low-frequency rTMS protocol produces an inhibitory effect on cortical excitability, while a facilitatory effect is

[2] The motor threshold is the lowest TMS intensity necessary to evoke MEP in a target muscle in 50% of trials [35]. The cortical silent period is referred to as the suppression of electromyographic activity (EMG) in the voluntarily contracted target muscle after the induction of a MEP [36].

often observed after a high-frequency rTMS protocol. Unfortunately, in these cases, the literature also often reports different and equivocal outcomes generated by the same rTMS protocol [5]. In general, now TMS is likely to be classified as a "brain-interference method" rather than a brain imaging method.

2.3. Methodological aspects of TMS-neuroimaging coregistration

Because of the electrical and magnetic principles TMS and neuroimaging are based upon, their simultaneous use (i.e., coregistration) poses several technical problems. The TMS pulse, in fact, induces an electromagnetic artefact that can affect data acquisition when it is performed during neuroimaging (i.e., "on-line" approach), especially when TMS is combined with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI). Such technical problems can mostly be avoided by applying rTMS before or after neuroimaging (i.e., "off-line" approach). Currently, with the exception of MEG, all the other neuroimaging techniques have been successfully used in combination with TMS, both in on-line and off-line approaches.

On-line and off-line approaches provide different information and pose different technical and methodological issues. The choice of one approach instead of the other is generally established based on the target of the study, as well as on the setting and the instruments available. The on-line approach allows direct evaluation of the instantaneous effect of magnetic stimulation on brain tissue. More specifically, TMS is used to interfere with ongoing neuronal activation whose variations in brain activity are detected by neuroimaging. Besides the information provided on the reactivity of the stimulated area and its connectivity to other areas, this approach also has potential value from a technical point of view since it permits researchers to clarify the interaction of TMS effect on the brain. One of the first examples of this kind of study was performed by Bohning and coworkers ([34] – discussed in section 3), who aimed to directly measure the exact magnetic field produced by TMS in human subjects. The authors used two TMS coils suitable for concurrent fMRI (i.e., constructed with non-magnetic materials) to map the magnetic fields generated by TMS in the human brain. This study was the first one that combined TMS and MRI in an on-line approach.

Off-line coregistration can be performed using neuroimaging before or after TMS. In the first case, neuroimaging can be used to guide the exact coil positioning in a localised brain area. This procedure is used particularly in cognitive neuroscience studies since neuroimaging techniques can reliably identify one or more brain areas that are activated during a cognitive task. Subsequent TMS can be applied over the identified area to interfere with ongoing neuronal processing while participants are performing a task that is supposed to involve the stimulated area. This procedure potentially provides important elucidation regarding the possible contribution to a cognitive process of a certain brain region or its interconnected areas. A famous study by Cohen and colleagues [30] provides a direct example of this approach. The authors based their work on previous neuroimaging studies on people who were blind from an early age, which showed prominent activation of the occipital visual

areas during Braille reading [37]. Starting with this evidence, they applied short trains of 10-Hz rTMS to different cortical areas in subjects who were blind from an early age while they were involved in the identification of Braille or embossed Roman letters. When TMS was delivered over the occipital visual cortex tactile perception was distorted, resulting in a large number of errors in both tasks. In contrast, the same stimulation in healthy volunteers affected their visual performance, but not their tactile performance. These data confirmed that blindness from an early age generates a cross-modal reorganisation that causes the recruitment of the visual cortex in somatosensory processing. Neuroimaging techniques such as MRI can also be used to define specific anatomical targets based on individual brain images for subsequent TMS. With MRI-guided frameless stereotactic neuronavigation, precise coil placement can be obtained with a high degree of reproducibility across different sessions (e.g., [38] – discussed in section 2.1). This application will be further discussed in the section related to TMS-MRI coregistration.

A different application of the off-line approach consists of using neuroimaging after rTMS to investigate and map the long-term effects of the stimulation. This application offers important insights into functional cortical plasticity as well as elucidation of the TMS mechanism's after-effects. Since the spTMS and ppTMS effects are instantaneous, the only protocol suitable for this approach is rTMS, whose after-effects may last for a variable time. For this reason, neuroimaging should start quickly after the rTMS protocol to ensure that even short-duration after-effects were detected [39]. An example of this application is provided by Lee and colleagues [40]. The authors explored the effects on regional excitability caused by low-frequency rTMS over the primary motor cortex. The authors applied 1 Hz rTMS for 30 minutes, and then activation was mapped through PET at rest and during freely selected finger movements. The results showed an effect of rTMS both locally, with a major activation in the stimulated motor area, and throughout the brain regions engaged in the task. In summary, on-line and off-line approaches provide different insights into the TMS effects on brain activity and imply different methodological and technical precautions. However, the use of one approach does not exclude the other one; conversely, the utilisation of neuroimaging both before and after TMS is an optimal method to detect the effects of the stimulation on neuronal activity.

3. TMS-EEG coregistration

Neural activity generates electric as well as chemical signals. The electric signals generated from the simultaneous activity of large neuron populations can be detected and measured by electrodes applied on the scalp (usually placed according to the 10-20 system). Such signals can be recorded from the scalp since brain, skull, and scalp tissues passively conduct the electric (as well as magnetic) currents generated by the neurons' activity. The recording of tension variations between different electrodes is referred to as electroencephalography (EEG). One of the main EEG applications in clinical and in research settings is the detection of electric responses evoked by cognitive, motor, or sensorial processes. These responses are referred to as event-related potentials (ERPs). The time-varying magnetic field generated by the TMS pulse produces currents in the cortical layers of the brain and a subsequent

depolarisation of cell membranes so that action potentials are initiated after the ion channels are opened [17]. The subsequent post-synaptic activation can be recorded in the EEG. The analysis of EEG signals can be used to localise and measure the synaptic activations, thus allowing direct inferences about the reactivity of cerebral areas and their functional connectivity. The first published attempt to measure TMS-evoked brain responses was performed by Cracco and coworkers [41]. The authors recorded responses to TMS from the homologous area contralateral to the stimulation site with an onset latency of 9-12 ms. This study was the first attempt to examine cerebral connectivity by combining TMS and EEG. Three years later, the same research group used a cerebellar stimulation and recorded responses from the interaural line [12]. However, these early attempts were not replicated immediately, probably because of the various technical limitations. Indeed, voltage changes induced by the TMS pulse between scalp electrodes are six orders of magnitude larger than microvolt-level EEG signals [42]. Such high voltage levels can lead to the saturation of a standard EEG amplifier, which can last for hundreds of milliseconds. The subsequent development of TMS-compatible multi-channel EEG recording systems allowed the measurement of instant and direct neuronal effects of TMS from multiple scalp locations, which was impossible with previous technologies. The first study that used these systems was conducted by Ilmoniemi's group. Technical and methodological aspects relative to these systems will be discussed in section 2.3.

The main capacity of TMS lies in its ability to non-invasively interfere with brain activity by modulating the voltage over the membranes of the cortical neurons. In a complementary way, the main potential of concurrent EEG lies in its ability to measure the instantaneous cortical activation induced by TMS with a millisecond time scale, which is currently not possible with any other brain imaging method. Techniques such as PET, SPECT, and fMRI, in fact, are unable to detect the temporal sequence of increased cerebral activity with a sampling frequency similar to that of neural signal transmission because changes in blood flow and oxygenation take several seconds after changes in neuronal activity. On the other hand, EEG does not provide as accurate a spatial resolution as the other techniques do. The next section will address the nuts and the bolts of TMS-EEG coregistration, providing a detailed view of its characteristics and methodology.

3.1. Advantages of TMS-EEG coregistration

This section discusses how the combined use of TMS and EEG can provide precise details on both the initial activation of the stimulated area (i.e., cortical reactivity) and the subsequent spread to connected regions (i.e., cortical connectivity). Cerebral reactivity is defined by the response of a certain brain area to stimulation. Traditionally, TMS was used to assess the reactivity of areas that offer a peripheral marker of central excitability, namely the primary motor cortex and the primary visual cortex. When TMS is applied to the primary motor cortex, a muscle twitch is elicited, measurable with EMG. Similarly, when the V1 area is stimulated, the subject may perceive a moving/flashing phosphene. Excluding these two regions other areas of the cortex are behaviourally silent and their reactivity can be investigated only through the combined use of TMS and EEG. In TMS-EEG studies, cortical

reactivity is examined through an analysis of the characteristics of TMS-evoked potentials, such as latency, amplitude, scalp distribution, and waveform (e.g., [18]). These indices represent quantifiable markers of the cerebral neurophysiological state of the stimulated area [43]. In particular, the study of how cortical response varies across different physiological states and/or cognitive conditions is a topic of central interest in the literature. For example, different modulation of reactivity can be generated in comparing responses during a cognitive task and at rest (e.g., [44] – discussed in section 2.3) or in comparing different physiological states after a pharmacological treatment or a TMS protocol. A recent example of the latter application has been provided by Lioumis and coworkers [45]. In this study, the authors aimed to study the responses to TMS of the left primary motor cortex and the prefrontal cortex in a test-retest design. TMS was applied at three intensities in two sessions with a 1-week interval between them. Accurate repositioning of the coil was guaranteed by a neuronavigation system. The results showed high reproducibility in cortical responses after the two TMS sessions, providing evidence of the reliability of TMS-EEG investigation of cortical excitability changes in test-retest designs.

From a technical point of view, the study of how an area reacts to a TMS pulse might be useful in clarifying the effect of a single TMS parameter on brain activity. An example of this application is provided by Kommsi and colleagues [46]. The authors aimed to directly evaluate the effect of the stimulus intensity on TMS-evoked cortical responses. TMS was applied over the primary motor cortices of seven healthy volunteers at four intensities (60%, 80%, 100%, and 120% of MT). The results showed a similar distribution of the potentials for the four intensities, whereas an increment in response amplitude was observed with higher intensities. The evidence provided by the study offered interesting elucidations on the effects of stimulus intensity on TEPs. First, TMS can evoke measurable brain activity even at subthreshold intensities (60% of motor threshold); second, the analysis of the relationship between the stimulus and response potentially offered insights into the state of activation of the brain.

Connectivity studies with traditional TMS-EMG setup were limited to the investigation of motor-associated area interaction (i.e., with "twin-coil" stimulation – discussed in section 1.2). With the development of TMS-compatible multi-channel EEG, the study of connectivity in non-motor areas has become possible. In TMS-EEG coregistration studies, cerebral connectivity is evaluated by tracing the spread of TMS-evoked activity by reconstructing the activity-sources and/or based on the latency of EEG deflections. The first procedure is realised through the application of the minimum-norm estimate, which localises the source of the electric signals [47]. The first study that successfully applied this procedure was performed by Ilmoniemi group [17]. These authors applied TMS at a 0.8 Hz frequency over the primary motor and visual cortices of healthy volunteers. The spread of the TMS-evoked activity was traced using inversion algorithms that localised an immediate response locally to the stimulation. They observed that 5-10 ms after the magnetic pulse, the activation spread to the adjacent ipsilateral motor areas; furthermore, after 20 ms, activation reached the homologous regions in the opposite hemisphere. This activation pattern was observed stimulating both areas. The study by Ilmoniemi and colleagues was the first that provided

direct information about cortico-cortical connections through the use of TMS-EEG coregistration. In recent years, many other research studies have confirmed the results obtained by these authors, also providing important insights into the study of the spread dynamics of TMS-induced activity (e.g., [48,49] – discussed in section 2.2).

The analysis of the latencies of scalp-recorded EEG deflections offered a different approach in the investigation of cortico-cortical connectivity. The high temporal resolution of EEG allows the reliable identification of the temporal progress of TMS-evoked activity spread. This permits researchers to infer the causal relations of the TMS-evoked activation. An example of this procedure was provided by Iramina and colleagues [50]. The authors applied TMS at three different intensities (90%, 100%, and 110% of MT) over the cerebellum (20 mm above the inion) and recorded frontal positive potential deflections at Cz with a latency of 9 ms and at Fz with a latency of 10 ms. The results obtained by the authors offered a possible demonstration of occipito-frontal connectivity and, on the other hand, provided evidence of the reliability of TMS-EEG coregistration as a precise methodology in connectivity studies. To this end, a further demonstration of TMS-EEG feasibility has been obtained by examining changes in the spread of TMS-evoked activity while placing the coil over different sites. Kommsi and coworkers stimulated five sites in the left sensorimotor cortex of six healthy volunteers while they monitored responses throughout the brain [38]. To ensure the precise localisation of the anatomic locus of stimulation the authors used a frameless stereotactic method (see section 3). A consistent pattern of response both ipsilaterally and contralaterally was recorded with a latency of 17-28 ms. More important, contralateral responses showed consistent changes when different loci were stimulated. Two conclusions may be drawn from these data. First, the importance of coil positioning is critical since even a small shift in its position caused a different response. Second, the precise recording of ipsi- and contralateral responses revealed a corresponding high spatiotemporal resolution of TMS-EEG methodology in detecting the spread dynamics of TMS-evoked activity.

3.2. Methodological approaches

As suggested by Miniussi and Thut [43], TMS-EEG applications can be grouped into three approaches: inductive, interactive, and rhythmic. Within the “inductive approach” TMS-EEG coregistration is used to provide insights into the neurophysiological state of the brain through TEP analysis across different conditions. The “interactive approach” aimed to investigate the temporal course and the spatial spread of TMS-induced activity during cognitive performance. Finally, in the “rhythmic approach”, TMS is used as a technique to interact with oscillatory brain activity.

From an inductive approach perspective, TEPs are considered an index of the cerebral neurophysiological state in areas that does not produce a peripheral marker in response to a TMS pulse. TEP analysis has useful application in clinical and research studies as well as in technical studies. As discussed above, cortical responses evoked by TMS potentially offer important insights into brain activity both locally in the stimulated area and in connected

regions. More specifically, the inductive approach aims to infer brain activity dynamics focusing on TEP characteristics and distribution (e.g., [17,38]) without considering behavioural outcomes (which are more relevant in interactive approach studies). Rather, inductive studies are more interested in comparing conditions generated from different neurophysiological states of the brain (e.g., [48,49]). An interesting example of this approach has been provided by Massimini and colleagues, who aimed to investigate connectivity changes across different states of consciousness [49]. The authors applied TMS at a subthreshold intensity (90% of MT) over the rostral portion of the right premotor cortex of six healthy volunteers. The results revealed a critical difference in the spread of TMS-evoked activity between the state of wakefulness and non-REM sleep. A prominent spread of the activity from the stimulation site to ipsi- and contralateral areas was observed during quiet wakefulness. In contrast, during non-REM sleep, the authors observed a rapid decrease in the initial response that did not spread beyond the stimulation site. Thus, the authors concluded that states of consciousness are strictly related to cerebral connectivity efficiency (Massimini et al., 2005). The data provided by this study are a direct exemplification of TEP's potential to reveal important information on the local and distant spread dynamics of cerebral activity.

Regarding technical applications, TEP analysis in combination with a systematic and methodical manipulation of TMS parameters can potentially provide important information on which parameters (e.g., stimulation intensity, coil orientation) are the most effective in producing a certain neuronal modulation. As seen previously in this chapter, the studies by Kommsi group [38,46] provided direct evaluation of the effects of stimulation intensity and coil positioning. Another example of this approach was provided by Bonato and colleagues. The authors applied TMS over the left primary motor cortex of six healthy volunteers, varying the coil orientation. Two orientations were compared: one at 45 degrees with respect to the sagittal plane (which was found to be optimal by previous studies – [52,53]) and one at 135 degrees with respect to the sagittal plane. The authors found that the two orientations evoked a similar pattern of electric potentials but with different amplitudes. From a technical point of view, TMS-EEG can thus provide useful insights into the comprehension of the unclear neurophysiological correlates of the TMS parameters. Future research studies investigating the effects of other TMS parameters might provide important contributions regarding the real outcomes of TMS on brain tissue.

The TMS-EEG interactive approach aims to investigate "where, when and how TMS interacts with task performance" ([43] p. 252). Therefore, interactive approach studies are particularly relevant in cognitive neuroscience research since they aim to study how the effects of TMS correlate with behaviour. More specifically, this approach focuses on the precise determination of which areas are affected by the pulse (i.e., "where") during cognitive performance; the definition of the cognitive process timing course, which is the critical temporal interval in which TMS affects cognition (i.e., "when"); and, finally, the clarification of the TMS effect in terms of the facilitation or inhibition of task performance (i.e., "how"). One example of this approach was offered by a study from Taylor and coworkers [54]. The authors aimed to investigate a frontal-parietal network interaction

during a spatial attention task. TMS was applied in short trains of 5 pulses at a frequency of 10 Hz over the right frontal eye field (FEF). When rTMS was delivered during the cueing period, the authors found that the neural activity evoked by visual stimuli was significantly affected. In another study, the same group of research [55], applied a similar rTMS protocol (3 pulses at 10Hz) over the dorso-medial frontal cortex (dMFC) to test its role in conflict resolution through an Eriksen flanker task [56]. The results were interesting: when contralateral (right-hand) incongruent trials occurred, TMS disrupted performance by increasing error rates. Both the results of these studies offered clear anatomo-functional contributions to FEF [54] and to dMFC [55]. Moreover, they provided interesting data on TMS focality since in both studies no effects were observed after the stimulation of a control site that was physically closer to the target areas. In summary, this evidence offers a demonstration of the value of TMS-EEG coregistration as a reliable technique in the study of TMS effects during cognitive tasks with high temporal and spatial resolution.

The TMS technique has different applications in the study of cerebral oscillatory activity [9]. Currently, the rhythmic approach represents one of the most promising avenues for clarifying the TMS mechanisms of interaction with brain activity [57]. The rhythmic approach uses the capacity of TMS to interact with brain rhythms, allowing the opportunity both to investigate the meaning of rhythmical activity and to induce a synchronisation of cerebral oscillations. A study by Sauseng and colleagues offered an exemplification of the first aspect [58]. The authors of the study aimed to investigate the relation between 10 Hz oscillatory activity and cortical excitability. To address this question they applied TMS to the primary motor cortex of six healthy volunteers. Their results showed that when the pre-stimulation level of alpha power was low, an MEP was evoked more easily, and vice versa. Moreover, this effect occurred only at the stimulation site. The results of the study offered insight into the relation between motor cortex excitability and local alpha oscillations. In contrast, other studies have focused on the capacity of rTMS to induce a pattern of oscillatory activity. Brignani and colleagues, for example, investigated the effects of low-frequency rTMS on the EEG oscillatory activity [59]. The authors applied rTMS at a 1 Hz frequency over the primary motor cortex of six healthy volunteers. The results showed an increment in the alpha band related to the period of the stimulation. These data confirm the TMS capacity to induce a synchronisation of the background oscillatory activity locally to the stimulation site. The induction of a certain rhythm of brain oscillation might also have potential value in the cognitive domain. More specifically, brain oscillations at a certain frequency are induced, and then their effect can be tested during the performance of a cognitive task. If a systematic effect on performance is observed, an inference regarding the causal relation between brain rhythm and cognitive processes could be established [7]. Some studies have explored this possibility. In a study by Klimesch and coworkers [60], for example, the authors applied rTMS at individual alpha frequency (IAF) to influence the dynamics of alpha desynchronisation leading to an improvement of cognitive performance [61]. Repetitive TMS was delivered over the mesial frontal cortex (Fz) and the right parietal cortex (P6) while subjects performed a mental rotation task. The results confirmed the authors' hypothesis: rTMS improved task performance by enhancing the extent of alpha desynchronisation. This study, besides providing evidence of the rTMS capacity to interact

with cerebral rhythms, also demonstrated the functional relevance of oscillatory neuronal activity in the alpha band during cognitive processing. Recently, more studies have investigated a possible relation between alpha oscillations and cognition. In particular, recent research studies that used visual tasks identified a relation between the occipito-parietal alpha amplitude and the perception of visual stimuli (e.g., [62]). Therefore, the use of the rhythmic approach in TMS-EEG studies also appears promising in cognitive domain research, and in the future more cognitive processes needed to be investigated in relation to brain rhythms.

3.3. Technical issues

The simultaneous use of TMS and EEG, like the other TMS-neuroimaging combinations, poses several technical issues due to artefacts of different nature. In this part of the chapter, technical problems concerning the combined use of TMS and EEG will be discussed. The aim is to review the strategies developed so far to obtain a reliable EEG recording during TMS. As mentioned above, the main problem of this methodology is caused by the high TMS-induced electrical field, which can saturate recording EEG amplifiers.

A great portion of the studies that have analysed the EEG response to TMS have focused on the cortical response (TEP) evoked by a single pulse on the primary motor cortex at rest (e.g., [38,45,49,51,63-65]). The TEP components detected in most of these studies are: N15, P30, N45, N100, P180, and N280. The large number of studies that observed this pattern of TEPs demonstrated the high reproducibility of TMS-evoked deflections, contrary to motor-evoked potentials, whose amplitude is highly variable [66]. In spite of the high consistency of TMS-evoked EEG potentials, only the N100 is considered a "universal" response since it is the most evident, pronounced, and reproducible component evoked by TMS over the motor cortex (e.g., [45,49,63,64,67]). On the other hand, the occurrence of the other components can vary depending on TMS-related factors (e.g., coil positioning or orientation – [38,51]) as well as subjective-related factors (e.g., state of the cortex and state of consciousness – [67,49]). Different TMS parameters, for example, can determine a temporal shift in the potentials, even of a few milliseconds (e.g., [51,65]). Currently, the origin of TEPs is still unknown with the exception of the N45 component, which has been localised in the central sulcus (ipsilateral to the stimulation) and whose amplitude is directly related to the stimulus intensity [63].

Interestingly, most of the studies mentioned above were unable to detect cortical responses before 10-15 ms from the TMS pulse onset or even later. This latency period that precedes TEP recording is due to the high voltages induced by the TMS pulse between scalp electrodes. These currents can cause saturation of the amplifier, which might last hundreds of milliseconds before the system resumes working appropriately. Thus, all attempts to apply TMS during an EEG recording have faced these technical issues. In recent years, the development of new technologies and solutions has gradually led to an improvement of the temporal resolution of EEG recording during TMS. Such strategies can be divided in two types: on-line strategies, which consists of the creation of technologies that are able to avoid saturating the EEG amplifiers during TMS (e.g., [42]) and off-line strategies, which aim to remove artefacts once the coregistration is completed (e.g., [44,68]).

In 1997, TMS-compatible multi-channel EEG systems were introduced, allowing the instantaneous measurement of TMS effect on brain activity from multiple scalp locations. The 60-channel EEG system developed by Virtanen group [42], guaranteed its TMS-compatibility through the use of gain-control and sample-and-hold circuits, which permit the locking of EEG signals for several milliseconds (i.e., "gating period") immediately post-TMS. This technology avoids the saturation of the recording by preventing the passage of the artefact along the amplifier circuits. Such a blocking system is controlled by an external trigger, which is activated about 50 μs before the TMS pulse and is released 2.5 ms after the pulse. In the study performed by Virtanen group in 1999, the authors successfully recorded EEG responses while TMS was applied over FCz with an intensity of 100% and 120% of MT and a frequency of 1 Hz. In spite of the novelty value of this system, some problems remained unsolved. For instance, the gating period lasts much longer than the TMS pulse itself, which lasts only about 300 μs. This did not allow the recording of the signal immediately after the stimulation. Other TMS-compatible EEG amplifiers have been developed recently. In 2003, Iramina and colleagues ([50] - discussed in section 2.1) developed a 64-channel system based on a sample-and-hold circuit and were able to measure EEG activities 5 ms after the TMS pulse onset. Another system developed by Thut and coworkers [44] was based on a slew-rate limiter: this technology allowed continuous recording and prevented saturation during TMS. Today, new TMS-compatible EEG systems are able to avoid saturation due to TMS pulse, which results in a very short-duration artefact. This feature permits continuous EEG recording during TMS, allowing researchers to see what happens in the EEG signal around the TMS pulse. Bonato and colleagues ([51] – discussed in section 2.2), for example, used TMS-compatible DC amplifiers that were able to tolerate the high time-varying magnetic field induced by TMS. This characteristic allowed the recording of cortical response to TMS with high temporal and spatial resolution. In spite of the high temporal resolution recording provided by these new systems, some technical questions remain unsolved. For instance, it is still difficult to distinguish between the cortical and non-cortical (i.e., magnetic) currents that characterise at least the early part of the response after TMS [69]. All these considerations reflect the relevance that artefact investigation still has in the literature and its characterisation as a crucial factor to differentiate artefactual activity from cortical activity.

Off-line strategies, unlike on-line ones, aim at removing the artefact only after the complete acquisition of the TMS-EEG coregistration. This aim is achieved through the use of software strategies (i.e., algorithms, off-line filters) or experimental procedures. Off-line strategies have been developed recently: the first work that used a similar approach was performed by Thut group (see below). Two main approaches can be distinguished: a subtractive approach and a correctional approach. Both procedures although based on different logics aim to correct, reduce, or remove the TMS-induced electromagnetic artefact. In the subtractive approach, a template artefact is generated by delivering stimulation in a control condition (e.g., [44]) or applying TMS over a phantom (e.g., [64]). The subtraction of the template artefact from experimental data permits the isolation of the target response. The studies of Thut group [44,70], as mentioned above, were the first to use a subtractive approach that aimed to isolate cortical responses related to a visual task (VEPs). To this end, they created a

control condition in which TMS pulses were delivered at rest. This procedure permits the isolation of only the artefact without task-related responses. This condition was then subtracted from the visual task condition to isolate only the task-related TEPs. A similar procedure was followed by Bender and coworkers [64], who aimed to investigate the influences of cerebral maturation on TMS-evoked N100. The authors used a glass head dummy covered by a cloth soaked with water (simulating the impedances of skull and scalp, respectively) to generate a template artefact. The study of only the N100 component was permitted by subtracting phantom artefacts from human-evoked potentials.

The correctional approach comprises all procedures aimed at reducing or removing artefacts through the use of algorithms and off-line filters. These procedures are more common in technical studies, often performed by biomedical and computer engineering equipment (e.g., [68,71]). Morbidi and colleagues, for example, proposed an off-line Kalman filter as a new effective and low-cost strategy for artefact reduction [71]. The solution proposed by the author allowed the modelling of the dynamic components of TMS-EEG signal through the use of time-varying covariance matrices. The authors compared the dynamic Kalman filter with stationary filters such as the Wiener filter, concluding that the first one guarantees a more efficient deletion of TMS-induced artefacts while preserving the integrity of EEG signals around TMS pulses. Another example of artefact correction via software was performed by Litvak group [68]. The authors used a method developed by Berg and Scherg [73], originally applied for ocular artefact correction, based on a multiple-source approach. Using a set of artefact topographies, the authors constructed a source model and a set of brain topographies that consisted of multiple dipoles that model brain activity. From this source model a linear inverse operator was computed that decomposed the data into a linear combination of brain and artefact activities, which were subtracted from the data. The results showed that the modelled brain activity was not altered after the correction process. In summary, off-line procedures also potentially offer a wide range of possible solutions to clean EEG recordings from TMS artefacts. Nevertheless, since this approach is still in an early stage, other research studies are needed to develop and improve new ad hoc strategies that provide an optimal dissociation between cortical and artefactual TMS-related activity.

Besides the relevance of the aspects just discussed, many other factors play an important role in providing a reliable signal-to-noise EEG with concurrent TMS. These aspects are mainly referable to TMS (e.g., parameters of stimulation, stimulator devices[3]) and to EEG setup (e.g., electrodes, wires, cap). Recently, several research studies have investigated the effect of specific TMS parameters, such as TMS frequency, intensity, waveform (e.g., [69]), ISI (e.g., [65]), or coil orientation (e.g., [51]) on artefact characterisation. In their study, Veniero and colleagues manipulated several TMS parameters to observe their effect in the electromagnetic artefact amplitude and latency [69]. The authors compared three TMS devices (two biphasic and one monophasic), four types of figure-of-eight coils, ten intensities (from 10% to 100% of the maximum output), three frequencies (spTMS; rTMS at 5 Hz; rTMS at 20 Hz), and two sham conditions (i.e., performed with a placebo coil and with a

[3] TMS stimulators can be categorized into two types based on the waveform generated: monophasic and biphasic. Recent studies have underlined their different effects on neural tissue (e.g., [78,79]).

real coil turned over). Furthermore, EEG artefact generated by TMS delivered over the scalp was compared to the EEG artefact generated by TMS over two phantoms (i.e., a melon and a human knee). The authors found that the artefact produced by the magnetic pulse lasted approximately 5 ms after TMS onset in all conditions. Its duration, therefore, was not affected by different parameters of stimulation. In contrast, the artefact amplitude was higher when evoked by a monophasic pulse compared to a biphasic one. Other studies that manipulated the TMS ISI and coil orientation did not find a prominent effect of these parameters on cortical response except for minor variations in the latency of some components [65,51].

Regarding EEG-related factors, the type of electrode is one of the most influential variables in performing an efficient TMS-EEG coregistration. Because of the strong electric field generated by TMS, an electrode suitable for TMS-EEG coregistration should satisfy numerous physical requirements to work appropriately. Small dimensions are necessary, first to prevent the forces caused by the induced currents from affecting the electrode too much, and second to avoid overheating. Moreover, to provide the best interface with the skin, it should be coated with a suitable surface material [73]. For these reasons, traditional electrodes (made of silver or tin and with a diameter of ~1 cm) are not suitable for concurrent TMS since they are more affected by the induced currents. This can result in both a larger artefact and a higher risk of skin burns [74-76]. Additional problems can result from electrode polarisation, caused by electric currents between the electrolyte and the electrode. When an electrode is polarised, the artefact might cause an EEG baseline shift that can last for hundreds of milliseconds. Currently, the most frequently used electrodes in TMS-EEG systems are small Ag/AgCl pellet electrodes. These characteristics, other than reducing temperature by more than 50% [73,77], permit excellent recording during TMS [77]. Another technical aspect that influences the artefact amplitude is electrode impedance which has to be kept at low values (generally below 5 kΩ). High values of impedance in fact can lead to greater artefacts [73]. Generally, low values of electrode impedance are reached with skin scrubbing and cleaning with alcohol or ad-hoc products, and several strategies may be implemented to achieve this result. A study conducted by Julkunen and colleagues, for example, found a significant reduction of TMS-induced artefacts after puncturing the epithelium under the electrode contacts with custom-made needles [80]. Finally, recent studies have observed that the electrode wire arrangement can also play an important role in reducing TMS-evoked artefacts (e.g., [69,81]). Sekiguchi and coworkers, in particular, tested the effect of coil direction relative to the orientation of the stimulated electrode wire [81]. The authors observed a great reduction in the artefact amplitude when the coil was placed perpendicularly to the wire direction of the stimulated electrode. Their results suggested that the rearrangement of the lead wires relative to the fixed coil orientation can significantly reduce TMS artefacts from EEG recordings.

Besides the electric effect on the brain, TMS application can affect EEG recording also as a result of multimodal sensory stimulation. A TMS pulse, in fact, has multiple "indirect" effects; for instance, it produces a "click" of 100-120 dB [82] that elicits an auditory response which, in turn, might produce a startle reflex that can affect behavioural data, especially in

reaction time detection [83]. Furthermore, there is evidence of auditory and sensorial-evoked potentials related to the TMS click that should be considered and controlled for, especially in the electrophysiological analysis of TMS evoked-potentials [84,85]. A solution to avoid this problem is using earplugs or masking the coil click with white noise (e.g., [63,86]) or a sound with a similar spectral content (e.g., [49]). Alternatively, if the experimental design does not allow the use of earplugs, some authors have created a control condition to isolate and exclude the auditory artefacts (e.g., [64]). Finally, TMS-elicited muscle activity (e.g., involuntary stimulation of a facial nerve) or electrode movement can also be source of artefacts during EEG recording. In these cases only slight modifications of the setting can improve the record, for instance by reorienting the coil, reducing the intensity, or trying to avoid direct contact of the coil with the recording electrodes.

3.4. Clinical applications

Electromiographic activity alterations induced by TMS, such as the prolongation of the silent period, have been used as an index in several neurological and psychiatric conditions and reported in patients with Parkinson's disease, dystonia, and Alzheimer's dementia [87,89]. The evaluation of cortical oscillatory activity extended and fostered the relevance of TMS-EEG coregistration, particularly focusing on the non-motor regions of the cortex (e.g., the prefrontal cortex – [59,90]). Moreover, differences between healthy and pathological patterns were reported in patients with schizophrenia [91,92]. The combined use of the TMS-EEG method by Manganotti group, interestingly, proved to be effective during sleep state and has inspired many works devoted to studying clinical samples [93]. Another example is provided by the group of Massimini and Tononi, who investigated cortical effective connectivity during loss-of-consciousness states [49,94]. These research studies are relevant in that they could be used for both diagnostic aims and treatment in pathologies related to minimally conscious states as well as in communication disorders such as aphasia, akinetic mutism, and catatonic depression.

A remarkable application of combined TMS-EEG involved pathologies (e.g., epilepsy, migraine) that are commonly excluded from TMS application. Manganotti group [95,96] evaluated the effects of sleep deprivation on cortical reactivity to TMS in patients suffering from juvenile myoclonic epilepsy (JME). They administered single-pulse TMS over the left motor area during continuous EEG recording, assessing TMS-evoked responses during waking, sleep deprivation, and different sleep stages. In these patients, sleep deprivation produced increased short-latency intracortical facilitation and decreased inhibition of motor areas, as well as, *de facto,* an overall increase in corticospinal excitability. In JME patients, the frontal excitability is a distinctive trait since it behaves in the opposite way with respect to the response to sleep deprivation in healthy controls, which is reduced. However, most studies have evaluated EEG states before and after a TMS treatment (e.g., epilepsy or migraine – [97,98]).

4. TMS-MRI coregistration

Magnetic resonance imaging (MRI) is an imaging technique based on the properties of the atomic nuclei of biological tissues. This technique measures their spin precession within a strong magnetic field induced by the MRI scanner. More specifically, the MRI-induced magnetic field causes an alignment of some atomic nuclei in the body parallel to the magnetic field itself. The radio frequency fields subsequently applied systematically perturb the alignment of the magnetised nuclei in a predictable direction. The rotating magnetic field produced by the nuclei is detectable by the MRI scanner, which records this information to construct an image of the scanned area. The images generated by an MRI scanner have a high spatial resolution of a few millimetres and provide detailed structural information on brain anatomy. However, since this method provides only static information, only a few research studies have focused on the simultaneous use of TMS and MRI. Most of the studies acquired TMS and structural data separately in time (i.e., by the off-line approach), avoiding most of the technical problems that characterise on-line coregistration.

The main technical problem in performing simultaneous TMS-MRI coregistration lies in the presence of the coil within the MRI scanner since it is made of ferromagnetic material. New MRI-compatible coils are suitable for concurrent MRI and fMRI since they are not made of magnetic material. The first study that used this kind of coil was performed by Bohning and colleagues [34]. The authors could measure and characterise the magnetic field generated by TMS in healthy human brains using a standard 1.5 T MRI scanner. Specifically, they obtained 3D maps of the magnetic field created by two TMS coils.

The combined use of TMS and MRI can have useful applications for both research and clinical purposes. Since TMS, as stated above, provides precious insights into the physiological state of brain regions, such information, if appropriately combined with detailed images provided by an MRI scanner, might reveal important correlations between physiological indices (e.g., cortical reactivity and connectivity) and structural measures. An example of this kind of study was provided by Boorman and coworkers [99]. The authors investigated the relationship between a physiological measure of functional connectivity and a measure of structural connectivity during the execution of a decision-making test. Functional connectivity was investigated (i.e., through a twin-coil approach – see section 1.2) by applying TMS over the dorsal premotor cortex and the primary motor cortex. The structural anatomic network, linking the brain regions involved in the task, was reconstructed using diffusion-weighted imaging (DWI). The results of the study revealed a relationship between individual differences in functional and structural connectivity in action choice-related brain networks. The potential contribution of TMS-MRI combined use in revealing possible correlations between physiological data (i.e., provided by TMS) and structural data (i.e., provided by MRI) is also evident in clinical studies. A study by Sach and colleagues, for example, used TMS capacity to non-invasively investigate the central-motor conduction in relation to changes in tissue structure due to the degeneration of corticospinal fibres, detected by MRI [100]. The authors applied single-pulse TMS over the

primary motor cortex of fifteen patients with amyotrophic lateral sclerosis (ASL), six of whom had no clinical signs. The results showed a negative correlation between central-motor conduction time and fractional anisotropy. This evidence offered insights into the diagnosis of motor neuron disease before clinical symptoms become apparent.

Regarding off-line TMS-MRI combined applications, these might not be strictly considered as coregistration approaches. However, the use of MRI imaging before TMS is highly popular especially in cognitive neuroscience research to perform neuronavigated TMS (for a recent review, see [101]). This procedure consists, first, of the acquisition of high-resolution structural images. Then, the subject's head outside the scanner is co-registered to MR images based on anatomical landmarks that are easily identifiable such as nasion, inion, and auricular deflexions. This permits precise guidance for the placement of the TMS coil over a particular brain region based on the subject's anatomy. Moreover, such a system allows on-line control of the TMS position, which can be monitored and fixed during a session of stimulation. Therefore, the highly reproducibility of TMS positioning and orientation across different sessions is guaranteed. In current cognitive neuroscience studies that use TMS, as stated before, the use of neuronavigation systems is now very common, even with the use of an MRI template, in case subjects do not have personal MRI scans.

5. TMS-fMRI coregistration

Functional magnetic resonance imaging (fMRI) is a functional imaging technique that uses magnetic resonance imaging to detect and measure the activation of a brain area. This procedure consists of the image of variations in regional blood flow, measured by changes in endogenous oxy- and deoxyhemoglobin concentration, which reflect the energy use of brain cells. The detection of such variations is based on the magnetic properties of deoxyhemoglobin and oxyhemoglobin, which are paramagnetic and diamagnetic, respectively. The local magnetic field variations caused by the quantity of oxygen in haemoglobin are detected by fMRI, offering a measure of the activation of a certain brain area. As mentioned above, fMRI is able to detect the activation of certain brain regions with high spatial resolution (i.e., with millimetre precision) and poor temporal resolution since changes in blood flow last longer than the underlying neural responses (i.e., a few seconds).

The combined use of TMS and fMRI is a promising methodology in determining the limitations of both techniques, as stated in section 1 of this chapter. However, the simultaneous use of the two techniques is technically challenging because of the high magnetic field strength of MRI scanners, which can vary from 1.5 to 7 T. The mere presence of TMS coils within the scanner can affect the homogeneity of the fMRI static magnetic field. This problem can lead to a signal loss in echo-planar images as well as spatial distortions. A recent study by Bungert and coworkers used some shims made of thin patches of austenitic stainless steel to reduce the effect of the TMS coil on the magnetic field [102]. The results showed a reduction of about 80% of the effect of the coil, which permitted the elimination of the associated artefact. Many technical problems arise from the simultaneous functioning of TMS and fMRI. A TMS stimulator, for example, may generate radiofrequency noise that can

affect the MRI signal. This problem is generally managed through the use of radiofrequency filters [39]. Recently, another type of image artefact generated by leakage currents in a TMS system was investigated by Weiskopf and his group [103]. The authors characterised the image artefacts through the use of numerical simulations and the application of different coil geometries in phantom studies. The problem was solved by devising a relay-diode combination that was inserted in the TMS circuit, reducing the leakage current. Furthermore, as in TMS-EEG coregistration, the TMS pulse itself can be a source of different artefacts during fMRI. Distortions caused by the TMS pulse were investigated at 2.0 T by Bestmann and colleagues [104]. The authors found that both the echo-planar imaging section orientation (EPI) relative to the plane of TMS coil and the temporal gaps between TMS and image acquisition play a crucial role in artefact generation. Based on the results of the study, the authors concluded that TMS should be applied at least 100 ms before EPI to avoid stimulation during imaging. To our knowledge, the first study that demonstrated the feasibility of TMS application during fMRI acquisition was performed by Bohning group. The authors used non-ferromagnetic TMS coil to stimulate the primary motor cortex of three healthy volunteers inside a 1.5 T MR scanner. They observed significant responses in the motor cortex during the TMS condition compared to a rest condition, proving that the combined use of the two techniques is possible.

Besides the technical issues posed by the simultaneous use of TMS and fMRI, this methodology has potential value for different purposes. The on-line coregistration of the two techniques might reveal the effect of TMS in neural circuits with respect to its spatial resolution, which is provided by MRI with high precision. This procedure can be performed at rest with the aim of investigating the basic mechanism of TMS-brain interaction and measuring the reactivity and connectivity of stimulated areas for neurophysiological applications. One example of these applications was provided by Bestmann and collaborators [107]. The authors applied high-frequency rTMS (3.12 Hz) over the left sensorimotor cortex of healthy volunteers. They compared stimulations with intensities above and below the active motor threshold of the subjects. The two intensities produced different results: suprathreshold rTMS produced high activation in the stimulated area (sensorimotor cortex) and in its connected regions, both cortical (supplementary motor area, dorsal premotor cortex, cingulate motor area) and subcortical (putamen, thalamus), whereas subthreshold rTMS elicited a similar pattern of activation but no MRI-detectable activity in the stimulated sensorimotor cortex. These results, on one hand, offered insight into the cerebral motor system's connectivity and reactivity; on the other hand, they showed interesting evidence regarding the TMS mechanisms of action regarding its different dynamics depending on the stimulation. Interestingly, its effects spread not only in cortical areas but also in subcortical structures.

Concurrent TMS-fMRI studies also potentially provide contributions to cognitive neuroscience research. TMS applied during a task permits establishment of the causal role of an area within a cognitive process. This inference can be reinforced by mapping with high spatial resolution the TMS-induced activity through concurrent fMRI. Sack and coworkers,

for example, investigated the role of the parietal cortex in visuospatial judgements [107]. The authors applied TMS to the left and right parietal cortices during fMRI while the participants performed a visuospatial task. The behavioural results revealed impaired performance when TMS was applied over the right parietal cortex, whereas left stimulation produced no effect. Furthermore, fMRI detected a change in the activity of a specific fronto-parietal network in the right hemisphere, which had a significant correlation with the impaired cognitive performance. This result revealed a specific right fronto-parietal activation during the task, corroborating the previous hypothesis of a distributed fronto-parietal network underlying visuospatial processes.

Useful applications can also be obtained using rTMS and fMRI separately in time (i.e., off-line approach). In a study performed by Tegenthoff and colleagues, for example, the authors aimed to investigate the effects of high-frequency rTMS in tactile perception as well as in cortical plasticity [108]. rTMS was applied at a frequency of 5 Hz over the cortical representation of the right index finger of the primary somatosensory cortex. Stimulation of this area caused a lowering of the discrimination threshold of the right index finger. This data was corroborated by subsequent fMRI, which detected an enlargement of the right index finger's somatotopic representation. The results obtained by the authors provided evidence of the effects of rTMS on perceptual as well as on cortical plasticity. Concurrent TMS-fMRI can, thus, have potential in establishing causal links between cognition, perception, motor processes and their cortical correlates.

Clinical applications of TMS-fMRI coregistration have mainly focused on the long-term effects of either a cerebral dysfunction or a rehabilitation program. The residual cortical activity was considered to be a variable indicating cerebral plasticity. Several studies conducted by Li's group were devoted to evaluating the cortico-cortical network in depressant patients and the influence of medications on this network. In their first study, Li and colleagues administered cycles of 1 Hz rTMS on the prefrontal cortex, interleaving fMRI measurements of the regional changes in BOLD response [109]. Through principal component analysis (PCA), they were able to describe the network of brain areas that increased activity, which included the stimulated area as well as deep limbic regions, critical in the treatment of depression. Later, these authors applied the stimulation in a temporal window after administering lamotrigine and valproic acids and demonstrated the reliability of TMS-fMRI coregistration in the assessment of the effect of medications both locally and in cortical networks [110]. Hamzei and coworkers assessed the effects of rehabilitative therapy after a stroke (of either the middle cerebral artery or internal capsule) that involved the motor functions of the hand area [111]. Paired pulse was applied to investigate intracortical inhibition and intracortical facilitation; BOLD response was measured following passive and active movements of either the affected or the non-affected hand. Their study was important since it was the first one to investigate the efficacy of a treatment using a multiple-view perspective obtained from several techniques. Although appealing, this kind of study is really rare, perhaps because of the several challenges posed by the combination of these methods.

6. TMS-PET and TMS-SPECT coregistration

The functioning of PET is based on the detection of pairs of gamma rays generated by the collision of positrons (emitted by an isotope that is introduced into the body as a tracer) with electrons. Through the detection of the exact points where gamma rays are generated, PET allows the reconstruction of three-dimensional images of tracer concentration within the body. Different radioactive tracers (e.g., carbon-11, oxygen-15) provide different indices, such as the regional cerebral blood flow (rCBF), which are strictly related to neuronal activity. Thus, PET images are able to detect selective activations of the brain both at rest and during a task with a spatial resolution of about 5 mm. Like PET, SPECT is a nuclear medicine tomographic imaging technique whose functioning is based on gamma ray detection. Since the two techniques are very similar, their combined use will be discussed together.

As far as we know, the first study that applied TMS during PET was performed by Paus' group [112]. In this study, the authors tested previous evidence of anatomical fronto-occipital connectivity provided by studies on monkeys [113]. Transcranial magnetic stimulation was delivered over the left frontal eye fields (FEF) in different trains of pulses (5, 10, 15, 20, 25, and 30 trains) at a frequency of 10 Hz with an intensity at 70% of the maximum output of the stimulator. The authors found a significant positive correlation between the number of TMS pulses and cerebral blood flow. More specifically, prominent activation was found in the stimulation site in the left medial parieto-occipital cortex and in the left and right superior parietal cortices. The results corroborated previous studies that investigated FEF connectivity on macaque monkeys [113] and provided clear evidence of the reliability of the combined TMS-PET technique in the study of cerebral connectivity. As demonstrated by the above mentioned study, the use of TMS during PET poses fewer technical problems compared to other neuroimaging coregistrations. Moreover, TMS-PET combined use guarantees distinctive advantages. First, during PET acquisition, it is possible to monitor the coil positioning since it is clearly visible; this is not possible during fMRI acquisition. Furthermore, during PET, even long rTMS sessions can be delivered without temporal limits, allowing researchers to see the effect of the stimulation both in the stimulated area and in the connected regions. On the other hand, this also represents a limitation since PET is unable to detect the effects of a single-pulse TMS or even of a short sequence of pulses. Therefore, because of its poor temporal resolution, only cumulative rTMS effects on brain activity can be detected by a PET scan [39].

Simultaneous TMS-PET coregistration has also been used in the study of cognitive processes. Motthaghy and colleagues, for example, tested the effect of rTMS on a working memory task and on regional blood flow changes [114]. Repetitive TMS was applied in 30 s trains at a frequency of 4 Hz over the dorsolateral prefrontal cortices (DLPFC) and over the midline frontal cortex as a control site. In the same time, subjects were required to perform a verbal working memory task. The results showed worse performance on the task when the stimulation was applied over the left and right DLPFC. Concurrently, significant reductions in regional blood flow changes were detected both locally and in connected regions. The

results obtained by the authors represent one of the first direct evidence showing the disruptive effects of rTMS in a cerebral region within a network involved in a cognitive task. Other studies have focused on rTMS effects on motor cortical excitability, offering interesting elucidation regarding its neurophysiological mechanisms; an example of this approach was provided by Lee's group [40], whose study was discussed in section 1.3.

Regarding therapeutic applications, few studies have used TMS-PET coregistration for clinical purposes. The PET and SPECT techniques are suitable for detecting changes in plasticity due to the TMS therapy, especially given that rTMS has mostly been used with patients resistant to pharmacological treatments. As a consequence, a relatively large body of literature on mood disorders, such as depression, has allowed the mapping of long-lasting activity changes and cortical reorganisation [115-117]. Frontal-lobe rTMS was also proposed as a treatment for Parkinson's dementia: studies conducted by Straffella's group tried to determine the modification caused by rTMS in the cortical functioning and in the neurotransmitters tied to the development of this kind of dementia [118]. Apart from these examples, the situation clearly suggests that TMS combined with these techniques for clinical purposes is limited to the study of the long-lasting effects of the TMS technique itself. Therefore, in the future, there will probably be no attempts to apply the simultaneous recording of PET/SPECT with TMS.

7. TMS-NIRS coregistration

Near-infrared spectroscopy (NIRS) is a spectroscopic method of detecting changes in haemoglobin concentrations through the measurement of the absorption of near-infrared light by neural tissue. This permits the detection of changes in brain activity with good spatial resolution, limited to the cortical regions. Since this method does not make use of magnetic fields, it is suitable to be combined with TMS without particular technical precautions. However, compared to other TMS-neuroimaging coregistrations, a smaller number of studies have used NIRS during TMS; therefore, technical details regarding this coregistration are still lacking.

One of the first studies that successfully applied TMS during NIRS was performed by Oliviero and colleagues [119]. The authors compared cerebral variations in oxyhemoglobin, deoxyhemoglobin, and cytochrome oxidase-induced magnetic and electrical stimulation. Stimulation was delivered at a frequency of 0.25 Hz over the NIRS probe on the anterior right frontal region. Repetitive TMS immediately induced a significant increase in oxyhemoglobin and a decrease in cytochrome oxidase, whereas this effect was not observed after electrical stimulation. The results of the study underlined the different effects provided by magnetic and electric stimulation, suggesting that rTMS induced higher regional cerebral blood flow rate and, consequently, an increase in the activation of the stimulated area. Interestingly, some studies have also evaluated the effect on metabolic activity after single-pulse TMS (e.g., [120,121]), which is otherwise impossible with other neuroimaging techniques such as PET and SPECT (see section 5). In a study by Mochizuki and coworkers, for example, the authors applied single-pulse TMS over the left primary motor cortex at

different intensities (100%, 120%, or 140% of the active motor threshold) both at rest and during contraction of the right first dorsal interosseous muscle [121]. The results showed an increase in oxyhemoglobin in the active condition when TMS was delivered at 100% intensity. In contrast, significant decreases in deoxyhemoglobin and total haemoglobin were observed under the resting condition with TMS at 120% and 140% intensity. The authors interpreted the decrease as a lasting inhibition induced by higher-intensity TMS that results in a reduction in the baseline firing of corticospinal tract neurons. Moreover, combined TMS-NIRS studies have also evaluated the effect of rTMS at higher frequencies such as 1 Hz (e.g., [122]) and theta-burst stimulation[4] (e.g. [123]), on the regional cerebral haemoglobin rate.

However, compared to the other techniques NIRS is a very new methodology. Therefore, more studies are needed in this field. Clinical research, for example, is lacking at the moment, but all indications suggest that this combination would be a worthwhile field of application for several pathological conditions (e.g., learning disabilities).

8. Conclusions

The combined use of different neuroimaging techniques is currently one of the most promising methodological approaches to the study of human brain functioning. Neuroimaging and TMS represent two complementary methodologies whose combined use is likely to be more widespread in the future. In this chapter, we have stressed the high potential of this integrative trend, as shown by the large number of studies discussed. Nevertheless, besides the fascinating perspective opened by the coregistration approach, several technical problems have limited advancement in some application fields. Therefore, many of the studies mentioned aimed to solve such technical problems. Once a reliable technical basis is established, many of the unsolved questions will be answered and future perspectives deepened. Specifically, more studies are needed to explore the clinical potential of a coregistration approach concerning both diagnostic and rehabilitation applications. Furthermore, the TMS-neuroimaging methodology also has great value in neuroscience research. Some recent applications, such as TMS-EEG rhythmic approach, might provide precious insights into the brain-cognition-behaviour relationship.

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[4] Theta-burst stimulation is a high-frequency TMS protocol in which 3 pulses at 50 Hz frequency are delivered 5 times in a second for 20 or 40 seconds (for details see [124])

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9. References

[1] Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet, 1:1106-1107

[2] Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nat. Neurosci., 1:73-79

[3] Shapiro KA, Pascual-Leone A, Mottaghy FM, Gangitano M, Caramazza A (2001) Grammatical distinctions in the left frontal cortex. J. Cognitive Neurosci., 13:713–720

[4] Cappa SF, Sandrini M, Rossini PM, Sosta K, Miniussi C (2002) The role of the left frontal lobe in action naming: rTMS evidence. Neurology, 59:720-723

[5] Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Català MD (1998) Study and modulation of human cortical excitability with transcranial magnetic stimulation. J. Clin. Neurophysiol., 15:333-343

[6] Bestmann S (2008) The physiological basis of transcranial magnetic stimulation. Trends Cogn. Sci., 12:81-83

[7] Miniussi C, Ruzzoli M, Walsh V (2010) The mechanism of transcranial magnetic stimulation in cognition. Cortex, 46:128-130

[8] Walsh V, Rushworth M (1998) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia, 37:125-135

[9] Ridding MC, Rothwell JC (2007) Is there a future for therapeutic use of transcranial magnetic stimulation? Nat. Neurosci., 8:559-567

[10] Miniussi C, Pellicciari MC, Rossini PM (2010) New prospects of transcranial electrical stimulation (tES) from bench to bed side. Neuropsychological Trends, 8:31-35

[11] Walsh V, Cowey A (1998) Magnetic stimulation studies of visual cognition. Trends Cogn. Sci., 2:103-110

[12] Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB (1992) Cerebello-frontal cortical projections in humans studied with the magnetic coil. Electroencephalogr. Clin. Neurophysiol., 85:265-272

[13] Mottaghy FM, Hungs M, Brugmann M, Sparing R, Boroojerdi B, Foltys H et al. (1999) Facilitation of picture naming after repetitive transcranial magnetic stimulation. Neurology, 53:1806-1812

[14] Allen EA, Pasley BN, Duong T, Freeman RD (2007) Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science, 317:1918-1921

[15] Wagner T, Rushmore J, Eden U, Valero-Cabre A (2009) Biophysical foundations underlying TMS: Setting the stage for an effective use of neurostimulation in the cognitive neurosciences. Cortex, 45:1025-1034

[16] Miniussi C, Ruzzoli M, Walsh V (2010) The mechanism of transcranial magnetic stimulation in cognition. Cortex, 46:128-130

[17] Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R et al. (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport, 8:3537-3540

[18] Kähkönen S, Komssi S, Wilenius J, Ilmoniemi RJ (2005) Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: implications for rTMS treatment in depression. Psychopharmacology, 181:16-20

[19] Poldrack RA (2005) Can cognitive processes be inferred from neuroimaging data? Trends Cogn. Sci., 10:59-63
[20] Aguirre GK (2003) Functional imaging in behavioral neurology and cognitive neuropsychology. In: Feinberg TE, Farah MJ Behavioral neurology and cognitive neuropsychology, 35–46, McGraw-Hill pp. 35-46.
[21] Raichle ME (1998) Behind the scenes of functional brain imaging: a historical and physiological perspective. Proc. Natl. Acad. Sci. USA, 95:765–772
[22] Sack AT, Linden EJD (2003) Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. Brain Res. Rev., 43:41-56
[23] Schiff S, Bardi L, Basso D, Mapelli D (2011) Timing spatial conflict within the parietal cortex: a TMS study. J. Cogn. Neurosci., 23:3998-4007
[24] Rothwell JC (2010) Using transcranial magnetic stimulation methods to probe connectivity between motor areas of the brain. Hum. Movement Sci., 30:906-915
[25] Chen R (2004) Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp. Brain Res., 154:1-10
[26] Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A et al. (1993) Corticocortical inhibition in human motor cortex. J. Physiol., 471:501-519
[27] Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr. Clin. Neurophysiol., 85:355-364
[28] Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H et al. (2001) Interhemispheric facilitation of the hand motor area in humans. J. Physiol., 531:849-859
[29] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, The safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol., 120:2008-2039
[30] Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J et al. (1997) Functional relevance of cross-modal plasticity in blind humans. Nature, 389:180-183
[31] George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P et al. (1995) Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport, 6:1853-1856
[32] Koch G, Brusa L, Caltagirone C, Peppe A, Oliveri M, Stanzione P et al. (2005) rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. Neurology, 65:623-625
[33] Konishita M, Ikeda A, Begum T, Yamamoto J, Hitomi T, Shibasaki H (2005) Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy – A pilot study. Seizure, 14:387-392
[34] Bohning DE, Pecheny AP, Epstein CM, Speer AM, Vincent DJ, Dannels W et al. (1997) Mapping transcranial magnetic stimulation (TMS) fields in vivo with MRI. Neuroreport, 8:2535-2538
[35] Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ et al. (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots—basic principles and procedures for routine clinical application. Electroencephalogr. Clin. Neurophysiol., 91:79-92

[36] Fuhr P, Agostino R, Hallett M (1991) Spinal motor neuron excitability during the silent period after cortical stimulation. Electroencephalogr. Clin. Neurophysiol., 81:257-262
[37] Sadato N, Pascual-Leone A, Grafman J, Ibañez V, Deiber MP, Dold G et al. (1996) Activation of the primary visual cortex by Braille reading in blind subjects. Nature, 380:526-528
[38] Komssi S, Aronen HJ, Huttunen J, Kesäniemi M, Soinne L, Nikouline VV et al. (2002) Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin. Neurophysiol., 113:175–184
[39] Siebner HR, Bergmann TO, Bestmann S, Massimini M, Johansen-Berg H, Mochizuki H et al. (2009) Consensus paper: Combining transcranial magnetic stimulation with neuroimaging. Brain Stimul., 2:58-80
[40] Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RSJ et al. (2003) Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J. Neurosci., 23:5308-5318
[41] Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB (1989) Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr. Clin. Neurophysiol., 74:417-424
[42] Virtanen J, Ruohonen J, Naatanen R, Ilmoniemi RJ (1999) Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. Med. Biol. Eng. Comput., 37:322-326
[43] Miniussi C, Thut G (2010) Combining TMS and EEG Offers New Prospects in Cognitive Neuroscience. Brain Topogr., 22:249-256
[44] Thut G, Northoff G, Ives JR, Kamitani Y, Pfennig A, Kampmann F et al. (2003) Effects of single-pulse transcranial magnetic stimulation (TMS) on functional brain activity: a combined event-related TMS and evoked potential study. Clin. Neurophysiol., 114:2071-2080
[45] Lioumis P, Kičić D, Savolainen P, Mäkelä JP, Kähkönen S (2009) Reproducibility of TMS—Evoked EEG Responses. Hum. Brain Mapp., 30:1387-1396
[46] Komssi S, Kähkönen S, Ilmoniemi RJ (2004) The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum. Brain Mapp., 21:154-164
[47] Hämäläinen MS and Ilmoniemi RJ (1994) Interpreting magnetic fields of the brain: minimum norm estimates. Med. Biol. Eng. Comput., 32:35-42
[48] Kähkönen S, Kesäniemi M, Nikouline VV, Karhu J, Ollikainen M, Holi M et al. (2001) Ethanol modulates cortical activity: direct evidence with combined TMS and EEG. Neuroimage, 14:322-328
[49] Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science, 309:2228-2232
[50] Iramina K, Maeno T, Nohaka Y, Ueno S (2003) Measurement of evoked electroencephalography induced by transcranial magnetic stimulation. J. Appl. Phys., 93:6718-6720
[51] Bonato C, Miniussi C, Rossini PM (2006) Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG coregistration study. Clin. Neurophysiol., 117:1699-1707
[52] Mills KR, Boniface SJ, Schubert M (1992) Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalogr. Clin. Neurophysiol., 85:17-21

[53] Brasil-Neto JP, Cohen LG, Panizza M, Nilsson J, Roth BJ, Hallett M (1992) Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J. Clin. Neurophysiol., 9:132-136

[54] Taylor PCJ, Nobre AC, Rushworth MFS (2006) FEF TMS Affects Visual Cortical Activity. Cereb. Cortex, 17:391-399

[55] Taylor PC, Nobre AC, Rushworth MF (2007) Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation electroencephalography study. J. Neurosci., 27:11343-11353

[56] Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in nonsearch task. Percept. Psychophys., 16:143-149

[57] Johnson SJ, Hamidi M, Postle BR (2010) Using EEG to Explore How rTMS Produces Its Effects on Behavior. Brain Topogr., 22:281-293

[58] Sauseng P, Klimesch W, Gerloff C, Hummel FC (2009) Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. Neuropsychologia, 47:284-288

[59] Brignani D, Manganotti P, Rossini PM, Miniussi C (2008) Modulation of Cortical Oscillatory Activity During Transcranial Magnetic Stimulation. Hum. Brain Mapp., 29:603-612

[60] Klimesch W, Sauseng P, Gerloff C (2003) Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. European J. Neurosci., 17:1129-1133

[61] Neubauer A, Freudenthaler HH, Pfurtscheller G (1995) Intelligence and spatiotemporal patterns of event-related desynchronization (ERD). Intelligence, 20:249-266

[62] Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G (2008) Spontaneous fluctuations in posterior alpha-Band EEG activity reflect variability in excitability of human visual areas. Cereb. Cortex, 18:2010-2018

[63] Paus T, Castro-Alamancos MA, Petrides M (2001) Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur. J. Neurosci., 14:1405-1411

[64] Bender S, Basseler K, Sebastian I, Resch F, Kammer T, Oelkers-Ax R et al. (2005) Transcranial Magnetic Stimulation Evokes Giant Inhibitory Potentials in Children. Ann. Neurol., 58:58-67

[65] Ferreri F, Pasqualetti P, Määttä S, Ponzo D, Ferrarelli F, Tononi G et al. (2010) Human brain connectivity during single and paired pulse transcranial magnetic stimulation. Neuroimage, 54:90-102

[66] Kiers L, Cros D, Chiappa KH, Fang J (1993) Variability of motor potentials evoked by transcranial magnetic stimulation. Electroencephalogr. Clin. Neurophysiol., 89:415-423

[67] Nikulin VV, Kičić D, Kähkönen S, Ilmoniemi RJ (2003) Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur. J. Neurosci., 18:1206-1212

[68] Litvak V, Komssi S, Scherg M, Hoechstetter K, Classen J, Zaaroor M, et al. (2007) Artifact correction and source analysis of early electroencephalographic responses

evoked by transcranial magnetic stimulation over primary motor cortex. Neuroimage, 37:56-70

[69] Veniero D, Bortoletto M, Miniussi C (2009) TMS-EEG co-registration: On TMS-induced artifact. Clin. Neurophysiol., 120:1392-1399

[70] Thut G, Ives JR, Kampmann F, Pastor MA, Pascual-Leone A (2005) A new device and protocol for combining TMS and online recordings of EEG and evoked potentials. J. Neurosci. Meth., 141:207-217

[71] Morbidi F, Garulli A, Prattichizzo D, Rizzo C, Manganotti P, Rossi S (2007) Off-line removal of TMS-induced artifacts on human electroencephalography by Kalman filter. J. Neurosci. Meth., 162:293-302

[72] Berg P, Scherg M (1994) A multiple source approach to the correction of eye artifacts. Electroencephalogr. Clin. Neurophysiol., 90:229-241

[73] Ilmoniemi RJ, Kičić D (2010) Methodology for Combined TMS and EEG. Brain Topogr., 22:233-248

[74] Roth BJ, Pascual-Leone A, Cohen LG, Hallett M (1992) The heating of metal electrodes during rapid-rate magnetic stimulation: a possible safety hazard. Electroencephalogr. Clin. Neurophysiol., 85:116-123

[75] Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr. Clin. Neurophysiol., 108:1-16

[76] Tallgreen P, Vanhatalo S, Kaila K, Voipio J (2005) Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. Clin. Neurophysiol., 116:799-806

[77] Ives JR, Rotenberg A, Poma R, Thut G, Pascual-Leone A (2006) Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. Clin. Neurophysiol., 117:1870-1875

[78] Kammer T, Beck S, Thielscher A, Laubis-Hermann U, Topka H (2001) Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. Clin. Neurophysiol., 112:250-258

[79] Sommer M, Aràanzazu A, Rummel M, Speck S, Lang N, Tings T et al. (2006) Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. Clin. Neurophysiol., 117:838-844

[80] Julkunen P, Pääkkönen A, Hukkanen T, Könönen M, Tiihonen P, Vanhatalo S et al. (2008) Efficient reduction of stimulus artifact in TMS–EEG by epithelial short- circuiting by mini-punctures. Clin. Neurophysiol., 119:475-481

[81] Sekiguchi H, Takeuchi S, Kadota H, Kohno Y, Nakajima Y (2011) TMS-induced artifacts on EEG can be reduced by rearrangement of the electrode's lead wire before recording. Clin. Neurophysiol., 122:984-990

[82] Starck J, Rimpiläinen I, Pyykkö I, Toppila E (1996) The noise level in magnetic stimulation. Scand. Audiol., 25:223-226

[83] Terao Y, Ugawa Y, Suzuki M, Sakai K, Hanajima R, Gemba-Shimuzu K et al. (1997) Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. Exp. Brain Res., 115:541-545

[84] Nikouline V, Ruohonen J, Ilmoniemi RJ (1999) The role of the coil click in TMS assessed with simultaneous EEG. Clin. Neurophysiol., 110:1325-1328
[85] Tiitinen H, Virtanen J, Ilmoniemi RJ, Kamppuri J, Ollikainen M, Ruohonen J et al. (1999) Separation of contamination caused by coil clicks from responses elicited by transcranial magnetic stimulation. Clin. Neurophysiol., 110:982-985
[86] Fuggetta G, Pavone EF, Walsh V, Kiss M, Eimer M (2006) Cortico-Cortical Interactions in Spatial Attention: A Combined ERP/TMS Study. J. Neurophysiol., 95:3277-3280
[87] Di Lazzaro V, Oliviero A, Profice P, Dileone M, Pilato F, Insola A et al. (2009). Reduced Cerebral Cortex Inhibition in Dystonia: Direct Evidence in Humans. Clin. Neurophysiol., 120:834-839
[88] Levy R, Lozano AM, Lang AE, Dostrovsky JO (2010) Event-Related Desynchronization of Motor Cortical Oscillations in Patients with Multiple System Atrophy. Exp. Brain Res., 206:1-13
[89] Casarotto S, Määttä S, Herukka SK, Pigorini A, Napolitani M, Gosseries O et al. (2011) Transcranial Magnetic Stimulation-Evoked EEG/Cortical Potentials in Physiological and Pathological Aging. Neuroreport, 22:592-597
[90] Schutter DJ, Hortensius R (2011) Brain Oscillations and Frequency-Dependent Modulation of Cortical Excitability. Brain Stimul., 4:97-103
[91] Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C (2007) Working Memory Related Gamma Oscillations in Schizophrenia Patients. Int. J. Psychophysiol., 64:39-45
[92] Cho RY, Konecky RO, Carter CS (2006) Impairments in Frontal Cortical Gamma Synchrony and Cognitive Control in Schizophrenia. PNAS USA, 103:19878-19883
[93] Manganotti P, Fuggetta G, Fiaschi A (2004) Changes of motor cortical excitability in human subjects from wakefulness to early stages of sleep: a combined transcranial magnetic stimulation and electroencephalographic study. Neurosci. Lett., 362:31-34
[94] Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G et al. (2010) Breakdown in Cortical Effective Connectivity During Midazolam-Induced Loss of Consciousness. PNAS, 107:2681-2686
[95] Manganotti P, Bongiovanni LG, Fuggetta G, Zanette G, Fiaschi A (2006) Effects of Sleep Deprivation on Cortical Excitability in Patients Affected by Juvenile Myoclonic Epilepsy: A Combined Transcranial Magnetic Stimulation and EEG Study. J. Neurol. Neurosurg. Psychiatry, 77:56-60
[96] Del Felice A, Fiaschi A, Bongiovanni GL, Savazzi S, Manganotti P (2011) The Sleep-Deprived Brain in Normals and Patients with Juvenile Myoclonic Epilepsy: A Perturbational Approach to Measuring Cortical Reactivity. Epilepsy Res., 96:123-131
[97] Valentin A, Arunachalam R, Mesquita-Rodrigues A, Garcia Seoane JJ, Richardson MP, Mills KR et al. (2008) Late EEG responses triggered by transcranial magnetic stimulation (TMS) in the evaluation of focal epilepsy. Epilepsia, 49:470-480
[98] Bohotin V, Fumal A, Vandenheede M, Gérard P, Bohotin C, Maertens de Noordhout A et al. (2002) Effects of Repetitive Transcranial Magnetic Stimulation on Visual Evoked Potentials in Migraine. Brain, 125:912-922

[99] Boorman ED, O'Shea J, Sebastian C, Rushworth MF, Johansen-Berg H (2007) Individual differences in white-matter microstructure reflect variation in functional connectivity during choice. Curr. Biol., 17:1426-1431

[100] Sach M, Winkler G, Glauche V, Liepert J, Heimbach B, Koch MA et al. (2003) Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis. Brain, 127:340-350

[101] Sparing R, Hesse MD, Fink GR (2010) Neuronavigation for transcranial magnetic stimulation (TMS): Where we are and where we are going. Cortex, 46:118-120

[102] Bungert A, Chambers CD, Phillips M, Evans CJ (2012) Reducing image artefacts in concurrent TMS/fMRI by passive shimming. Neuroimage, 59:2167-2174

[103] Weiskopf N, Josephs O, Ruff CC, Blankenburg F, Featherstone E, Thomas A et al. (2009) Image artifacts in concurrent transcranial magnetic stimulation (TMS) and fMRI caused by leakage currents: Modeling and compensation. J. Magn. Reson. Imaging, 29:1211-1217

[104] Bestmann S, Baudewig J, Frahm J (2003) On the synchronization of trans- cranial magnetic stimulation and functional echo-planar imaging. J. Magn. Reson. Imaging, 17:309-316

[105] Bohning DE, Shastri A, Nahas Z, Lorberbaum JP, Andersen SW, Dannels WR et al. (1998) Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Invest. Radiol., 33:336-340

[106] Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2004) Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur. J. Neurosci., 19:1950-1962

[107] Sack AT, Kohler A, Bestmann S, Linden DEJ, Dechent P, Goebel R et al. (2007) Imaging the brain activity changes underlying impaired visuospatial judgments: simultaneous fMRI, TMS, and behavioural studies. Cereb. Cortex, 17:2841-2852

[108] Tegenthoff M, Ragert P, Pleger B, Schwenkreis P, Förster AF, Nicolas V et al. (2005) Improvement of tactile discrimination performance and enlargement of cortical somatosensory maps after 5 Hz rTMS. PLoS Biol., 3:e362

[109] Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS (2004) Acute Left Prefrontal Transcranial Magnetic Stimulation in Depressed Patients is Associated with Immediately Increased Activity in Prefrontal Cortical as well as Subcortical Regions. Biol. Psychiatry, 55:882-890

[110] Li X, Large CH, Ricci R, Taylor JJ, Nahas Z, Bohning DE et al. (2011) Using Interleaved Transcranial Magnetic Stimulation/Functional Magnetic Resonance Imaging (fMRI) and Dynamic Causal Modeling to Understand the Discrete Circuit Specific Changes of Medications: Lamotrigine and Valproic Acid Changes in Motor or Prefrontal Effective Connectivity. Psychiatry Res., 194:141-148

[111] Hamzei F, Liepert J, Dettmers C, Weiller C, Rijntjes M (2006) Two Different Reorganization Patterns After Rehabilitative Therapy: An Exploratory Study with fMRI and TMS. Neuroimage 31:710-720

[112] Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J. Neurosci., 17:3178-3184

[113] Schall JD, Morel A, King DJ, Bullier J (1995) Topography of visual cortex connections with frontal eye field in macaque: convergence and segregation of processing streams. J. Neurosci., 15:4464-4487

[114] Mottaghy FM, Krause BJ, Kemna LJ, Töpper R, Tellmann L, Beu M et al. (2000) Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. Neurosci. Lett., 280:167-170

[115] Speer AM, Kimbrell TA, Wassermann EM, D Repella J, Willis MW, Herscovitch P et al. (2000) Opposite Effects of High and Low Frequency rTMS on Regional Brain Activity in Depressed Patients. Biol. Psychiatry, 48:1133-1141

[116] Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P et al. (2009) Opposite Effects of High and Low Frequency rTMS on Mood in Depressed Patients: Relationship to Baseline Cerebral Activity on PET. J. Affect. Disord., 115:386-394

[117] Nadeau SE, McCoy KJ, Crucian GP, Greer RA, Rossi F, Bowers D et al. (2002) Cerebral Blood Flow Changes in Depressed Patients after Treatment with Repetitive Transcranial Magnetic Stimulation: Evidence of Individual Variability. Neuropsychiatry Neuropsychol. Behav. Neurol., 15:159-175

[118] Strafella AP, Ko JH, Grant J, Fraraccio M, Monchi O (2005) Corticostriatal Functional Interactions in Parkinson's Disease: A rTMS/[11C]raclopride PET Study. Eur. J. Neurosci., 22:2946-2952

[119] Oliviero A, Di Lazzaro V, Piazza O, Profice P, Pennisi MA, Della Corte F et al. (1999) Cerebral blood flow and metabolic changes produced by repetitive magnetic brain stimulation. J. Neurol., 246:1164-1168

[120] Noguchi Y, Watanabe E, Sakai KL (2003) An event-related optical topography study of cortical activation induced by single-pulse transcranial magnetic stimulation. Neuroimage, 19:156-162

[121] Mochizuki H, Ugawa Y, Terao Y, Sakai KL (2006) Cortical hemoglobin concentration changes under the coil induced by single-pulse TMS in humans: a simultaneous recording with near-infrared spectroscopy. Exp. Brain Res., 169:302-310

[122] Chiang TC, Vaithianathan T, Leung T, Lavidor M, Walsh V, Delpy DT (2007) Elevated haemoglobin levels in the motor cortex following 1 Hz transcranial magnetic stimulation: a preliminary study. Exp. Brain Res., 181:555-560

[123] Mochizuki H, Furubayashi T, Hanajima R, Terao Y, Mizuno Y, Okabe S et al. (2007) Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices. Exp. Brain Res., 180:667-675

[124] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta Burst Stimulation of the Human Motor Cortex. Neuron, 45:201-206