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Electroencephalography during Transcranial Magnetic Stimulation: current modus operandi

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1 Introduction

Transcranial magnetic stimulation (TMS) was originally developed as an alternative to the often unpleasant transcranial electric stimulation via surface electrodes attached to the skin (Barker et al, 1985). Today, TMS is widely used as a research device in both cognitive and clinical neuroscience and has recently been implemented in neurotherapeutics (Walsh and Cowey, 2000; Hummel and Cohen, 2006; Ridding and Rothwell, 2007; Fregni and Pascual-Leone, 2007; Miniussi et al., 2008). However, in order to take advantage of this method's full potential for brain research and therapeutic control, it is essential to understand its mechanisms of action. Although much can be inferred indirectly by the observation of TMS effects on behavior, direct insight into TMS action can only be obtained through the recording of neuronal signals during and after TMS. For instance, TMS not only has different effects depending on the stimulation parameters, but those effects might differ as a function of regions of the brain (Sack and Linden, 2003). Moreover, TMS effects are not limited to the targeted area but reflect the ability of the entire brain to cope with the local change (Sack, 2006). Ultimately, understanding how TMS acts upon the brain will help to more accurately interpret the induced behavioral consequences, e.g. in terms of network effects (Bestmann et al, 2008; Driver et al., 2009; Ruff et al., 2009), or their dependence on pre-TMS brain states (e.g. Silvanto and Pascual-Leone, 2008), etc. This will aid, in turn, in the overall understanding of the brain-behavior relationship and may well lead to the development of new therapeutic TMS protocols.

One method that can be used to explore neuronal signals and network dynamics in real-time during TMS is electroencephalography (EEG). Unfortunately, due to the TMS-induced magnetic field contaminating the brain signals, EEG recordings during TMS are not straightforward. The first measures of TMS-evoked brain responses using EEG were performed by Cracco et al. (1989), who used one scalp electrode to register responses to TMS over a cortical area contralateral to the stimulation site. Eight years later, a TMS-compatible EEG recording system was introduced, allowing measurement of TMS brain responses over

multiple scalp locations, including at the stimulation site (Ilmoniemi et al., 1997). In the last decade, further methodological improvements have been made and recording systems designed.

In this chapter, we provide a step-by-step guide to the methods of TMS-EEG. We first examine possible artifacts in the EEG recordings resulting from TMS (part 2). We define artifacts as any contamination of the brain signal of interest. Consequently, TMS-artifacts can be of electromagnetic nature (2.1.1) but also of mechanical (2.1.2) and physiologic origin (2.1.3). We will emphasize the difficulty in artifact avoidance (2.2) and illustrate the methods that have been applied to minimize these artifacts or isolate them from the brain signals of interest (part 3). We proceed by examining practical issues to consider before the TMS-EEG experiment (3.1), during experimentation (3.2-3.3), and after recording (3.4). A summary of the main points can be found in Table 1. Finally, we attempt to provide a survey of recent insights in the fields of cognitive and clinical neurosciences stemming from the TMS-EEG combination (see parts 4 and 5).

2 The TMS-EEG artifact(s)

2.1. Artifact types

2.1.1. The electromagnetic artifact

TMS is based on the phenomenon of electromagnetic induction. The transient, time-varying magnetic field (with a pulse-duration of around 100 microseconds) creates an electric field in the brain and subpopulations of neurons discharge in response. Unfortunately, the same phenomenon also affects every electrical circuit in the coil vicinity. For example, high voltage (on the order of several volts, Siebner et al., 2009) might be induced in the loops formed by disk- or ring-electrodes, the electrode leads, and amplifier circuits. This high voltage is a source of two problems: the first concerns safety, as traditional EEG electrodes overheat in the presence of strong induced (eddy) currents. The second concerns the acquisition of exploitable data. Traditional amplifiers, because of their design and wide-band characteristics, can respond to high-energy electric fields by saturating for many seconds or even minutes. This saturation conceals a large portion of the brain response to TMS (Ives et al., 2006, see Fig. 1). Some amplifiers may even become damaged due to the TMS pulse (Ives et al., 2006).

In the last decade, new EEG hardware has been designed that allows for safe EEG-recording in the magnetic field generated by TMS (or magnetic resonance imaging) without the risk of

electrode overheating and/or amplifier saturation. However, even with these new systems, recordings will be contaminated by TMS-induced electric artifacts to different degrees, depending upon the setup (system, electrode preparation, etc.). See Fig. 2 illustrating the variability in electric artifact size and duration over studies.

Induced voltage peaks and charges

The primary electromagnetic artifact generated by TMS consists of an immediate, brief, high-voltage peak. This artifact has a very high amplitude and can reach thousands of microvolts (see e.g, Veniero et al., 2009 and below). In addition, the electric field may induce charge-differences in the hardware circuitry, at the interface between the electrodes and the skin, and between skin layers (see Julkunen et al., 2008b for the latter). Such electrical charges will gradually decay over time which may contribute to a longer lasting artifactual deflection that can follow the initial voltage peak (e.g. Litvak et al., 2007; Thut et al., 2005).

Recharge artifact with repetitive TMS

After the initial voltage peak coincident with the TMS-discharge, a second artifactual peak might appear 5-70 ms after the TMS pulse when TMS pulses are applied in rapid succession during repetitive TMS (rTMS) (Veniero et al. 2009). This is created by the need for rapid recharge of the TMS device in rTMS protocols (Veniero et al., 2009). This artifact is of relatively low amplitude (on the order of 10 μ V) and occurs consistently at a fixed latency after the TMS pulse, depending on TMS intensity (longer latency for higher intensities, Fig. 3).

2.1.2. The mechanical artifact resulting from electrode motion

During EEG recordings, any movement of an electrode with respect to the skin surface mechanically disturbs the distribution of charge that is created at the skin-electrode interface. This results in a momentary change of the potential and is known as the motion artifact or movement artifact (Ilmoniemi and Kicic, 2010).

During TMS-EEG experiments, especially if the TMS coil is in contact with one or several electrodes, movement of those electrodes is almost unavoidable, causing a change in electric potential on the order of several millivolts. Even if the coil is not touching the electrodes, the electromagnetic effect of TMS might cause the movement of standard electrodes. According to Lorenz's law, "an induced current is always in such a direction as to oppose the motion or change causing it". Thus, the primary current in the coil, which creates the primary magnetic field responsible for brain stimulation, also creates a secondary current in the electrodes. This, in turn, creates a secondary magnetic field, opposed to the primary field. As a consequence, the coil and the electrodes exercise a repulsive force which can result in

electrode movement. Additionally, electrode motion can result indirectly from TMS-induced muscle contraction.

2.1.3. The physiologic artifacts

Scalp muscles may be activated by the TMS pulse directly or in response to the activation of nerves on the scalp. Muscle contractions cause strong artifacts (from hundreds to thousands of microvolts) in the electrodes located near the activated muscles. These artifacts are particularly prominent when stimulating frontal and temporal areas. Because muscle relaxation takes several tens of milliseconds (Ilmoniemi and Karhu, 2008), these artifacts often contaminate the brain signal of interest.

TMS might also trigger eye movements or blinks as a consequence of a startle caused by the loud click or discomfort associated with the pulse. Eye movements and blinks create a deflection of the potential mainly across channels of the forehead (ocular artifacts) depending upon the reference. This deflection is on the order of tens of microvolts and masks other physiological signals.

Finally, TMS can provoke sensory and cognitive evoked potentials. The former category consists of somatosensory-evoked potentials (SEP) and auditory-evoked potentials (AEP). SEPs are evoked by the tapping sensation on the scalp (caused by the vibration of the coil in contact with the head during the discharge), or by the stimulation of cranial nerves or the peripheral muscle contraction. AEPs are elicited by the loud click (transmitted via both air and bone conduction). The latter category (cognitive potentials) may be generated through orienting of attention to the TMS pulse for a more cognitive or emotional appraisal of TMS (e.g. monitoring of outcome). Such cognitive artifacts would be characterized by responses to TMS that originate in nonstimulated sites and are invariant to where over the scalp TMS is applied (see e.g. fronto-central theta-response in Hamidi et al., 2010 and Thut et al., 2011a, but see Garcia et al, in press). These artifacts can be mistaken for genuine TMS-induced activity as they reflect true brain signals and are, consequently, in the range of TMS induced brain responses.

2.2. Artifact-size(s), form(s) and duration(s)

Electromagnetic artifacts induced by TMS are easily discernable in raw continuous EEG data (Fig. 2). Their peak voltages can be estimated using Faraday's law of electromagnetic induction.

These artifacts are generated in every loop of the EEG circuit where an electromotive force ϵ might be induced. According to Faraday's law, this "force" (measure in volts) is:

$$\varepsilon = \oint_c E \cdot dl = - \frac{\partial \phi_B}{\partial t}$$

where E is the electric field, c the perimeter of the loop through which the magnetic field enters, ϕ_B the magnetic flux and t the time. The magnetic flux ϕ_B through the loop of surface S , created by the magnetic field \vec{B} , can be calculated from the following equation:

$$\phi_B = \iint_S \vec{B} \cdot d\vec{S}$$

The tension (voltage) between two electrodes, separated by a distance d can be estimated as the product between the electric field E and the distance d . An estimation of the TMS induced voltage U is thus:

$$U \propto \frac{\Delta B}{\Delta t} \cdot \frac{S}{c} \cdot d = \frac{\Delta B}{\Delta t} \cdot \frac{R}{2} \cdot d$$

where ΔB is the variation of the magnetic field (≈ 1 T), Δt the duration of the TMS pulse (≈ 100 μ s) and d the distance between two electrodes (≈ 2 cm). With a radius of the loop R of 1 cm, the voltage U would be in the order of 1000 microvolts. This is several orders of magnitude above physiological signals (such as spontaneous scalp EEG, task-evoked potentials, and TMS-evoked responses/potentials), which are generally inferior to 100 microvolts (see e.g. Paus et al., 2001).

Accordingly, most of the TMS-induced voltage is artifact and not brain signal. This can also be demonstrated by a simple experiment: recording EEG while TMS is applied with the coil touching the scalp (condition 1) or with a 1 cm thick sheet of plastic between the scalp and coil (condition 2). Discharging the coil over the hand motor cortex with TMS just above motor threshold evokes clear muscle twitches in condition 1 but rarely evokes any twitches in condition 2. This suggests more effective brain stimulation in the first as compared to the second case. Yet, the strong TMS-induced EEG-deflections do not show any clear difference between the two conditions (see Thut et al., 2005 using a low slew-rate limiting amplifier, see also part 3.1.2). As the measured voltages in the EEG are of similar amplitude in both cases, it has been concluded that many TMS-induced effects result from magnetically elicited contamination of EEG components (electrical contamination) rather than being of a physiological nature (Thut et al., 2005).

The electromagnetic portion of the artifact has also been evaluated through stimulation of a phantom head (Virtanen et al., 1999; Bender et al., 2005; Morbidi et al., 2007; Veniero et al., 2009), allowing characterization of the artifact in the absence of brain and muscular response (Fig. 4). This artifact depends on the TMS pulse form (e.g. monophasic or biphasic, see

Veniero et al., 2009; Julkunen et al., 2008b) but clearly differs from brain activity evoked by TMS. This discrepancy can be used to disentangle artifact from signal, e.g. when using independent component analysis for post-processing if required (see 3.4.4).

The artifact size, form, and duration may vary across different EEG settings. For instance, the exponentially decreasing DC-shift which often follows the immediate voltage peak (and which may reflect decay of TMS-induced charges, see 2.1.1.1) can span over several tens (Litvak et al., 2007) to several hundreds of milliseconds (Thut et al., 2005, Virtanen et al., 1999, Fig. 5), and will have to be eliminated by post-processing (Thut et al., 2003; Levitt-Binnun et al., 2010). With some TMS-EEG hardware, however, this slow decay is virtually absent and only the initial voltage peak is present, thereby shortening the TMS-EEG artifact considerably. The shortest artifact described thus far is of 5-8 ms duration, measured at a TMS intensity of about 60% of maximum stimulator output (Veniero et al., 2009; Thut et al., 2011a). Therefore, depending upon the system employed, different levels of artifact control will be required.

It has to be kept in mind, however, that there is currently no system which allows a completely artifact-free recording. Plus, mechanical and physiological artifacts might be present. Carefully choosing the hardware and designing the experiment is crucial to optimally minimize the recorded artifacts.

3 Methodology: how to minimize the TMS-EEG artifact

Procedures for the reduction of electromagnetic artifacts aim to minimize artifact size and duration by adapting the electrical properties of the circuits and/or electrodes while keeping TMS-intensity constant. This can be achieved through appropriate amplifier- and electrode-designs, wire arrangement, and skin preparation for optimizing electrode-skin impedance (see 3.1.1, 3.1.2, 3.2.1, 3.2.2). These designs also reduce the risk of electrode heating and therefore meet safety requirements (3.1.1). The recharge artifacts, on the other hand, may be eliminated by controlling the TMS machine (for delaying recharge artifacts see 3.2.3). Physiological artifacts can be reduced by experimental setup (sound masking, distraction task), or, if reduction is not possible, should at least be monitored (control conditions) (see 3.2.4-3.2.7). Finally, residual artifacts can be dealt with offline via post-processing (see 3.4).

3.1. Before the experiment: choosing suitable hardware

3.1.1. Electrodes

Note on safety: Electrodes may heat up after a few pulses, which is associated with a risk of skin burns. In standard disk electrodes, each pulse can increase temperature by 5°C (Ilmoniemi and Kicic, 2010). Thus, in a room at 20°C, 5 pulses are sufficient to exceed the recommended safety limit of 41°C for medical equipment (IEC-601, see Ilmoniemi and Kicic, 2010). Therefore, even in experiments where artifacts do not impede analysis (such as when the focus of the study is on EEG signals prior to TMS or signals several hundreds of milliseconds after TMS), one should be aware of the risk of burns and choose electrodes accordingly.

TMS-compatible electrodes should satisfy several criteria: they must (1) allow for a safe recording, (2) limit TMS artifacts (both achieved through electrode design in regards to diameter, type and material), and (3) allow for effective brain stimulation despite the offset of the coil from its ideal scalp position by the mounted electrodes (electrode-thickness). At the same time, the electrode should form a good electrical contact and impedance (resistance) should be kept as low as possible to allow for measuring of the electric potential on the skin.

It has been shown that both heating and force are proportional to the conductivity of the electrode material (Roth et al., 1992; Ilmoniemi and Kahru, 2008). The challenge is, therefore, to maintain high conductivity (for the accurate recording of scalp potentials) and simultaneously to prevent heating and force. To achieve this, one should ideally use small electrodes. This is because heat induction is proportional to the square of the electrode diameter (Roth et al., 1992). Likewise, the electromagnetic force (responsible for electrode movement) is proportional to the thickness of the electrode and the cube of its diameter (Ilmoniemi and Kahru, 2008). In addition, heating and force can be further reduced by the choice of special electrode designs and materials that minimize the current-loop area, the conductive mass of the electrodes, or both. This reduces TMS-induced eddy-currents in the electrodes, a source of heating and force. The current-loop area can be reduced by cutting a section out of silver ring electrodes (Roth et al., 1992). A slit in an annulus-shaped electrode reduces both heating and the DC-offset by an order of magnitude (see e.g. Virtanen et al., 1999 for a DC-offset reduction from 90 μV to 12 μV). The conductivity mass can be reduced by using conductive plastic pellet electrodes coated with a thin layer of silver epoxy to create an Ag/AgCl surface (Ives et al., 1998). Pellet electrodes lead to a drop in the DC shift below 1 μV (Virtanen et al., 1999, see Fig. 5). TMS-compatible electrodes are commercially available.

3.1.2. Amplifiers

A TMS pulse might saturate one or several amplifiers in a standard EEG system. The amplifiers might then take hundreds of milliseconds to recover, preventing the recording of brain signals. Different amplifiers or preamplifiers have been designed to tackle this issue.

Sample-and-hold circuits

The sample-and-hold solution (developed by Virtanen et al., 1999) uses amplifier-gain control and sample-and-hold circuits to prevent the strong TMS artifact from being transmitted to the filter circuits. A sample-and-hold circuit consists of at least one switch and one capacitor. When the switch opens, the capacitor keeps tension at the level prior to opening. In the system developed by Virtanen et al. (1999), gain-control and sample-and-hold circuits protect the amplifier at different input stages. The gain of a first amplifier is reduced during the TMS pulse while a switch sets the entrance of a second amplifier simultaneously to zero (limiting voltage inputs). Further downstream, two sample-and-hold circuits are blocked shortly before the TMS pulse and are released shortly after the pulse in order to maintain voltage at a constant level during TMS. To test performance of this system, Virtanen et al. (1999) have measured artifacts for a 2.5ms-gating period from electrodes attached to a phantom (styrofoam dummy head covered by a leather sheet moistened with physiological saline solution). During the gating period, the voltage peak was smaller than $\pm 1.7 \mu\text{V}$ in all channels. After gating, DC shifts were below $\pm 1.3 \mu\text{V}$ and $\pm 0.5 \mu\text{V}$ at 3 ms and 10 ms post-TMS respectively, with the exceptions of three channels directly under the coil. This system has been commercialized. Typically, gating periods start at 0.05-0.1 ms pre-pulse and end at 2-20 ms post-pulse (Tiitinen et al., 1999; Kahkhonen et al., 2001; Komssi et al., 2004; Kahkhonen et al., 2005; Esser et al., 2006; Massimini et al., 2007; Hamidi et al., 2010). The shortest gating period ever tested was 100 μs by Ilmoniemi et al. (1997). The circuit may require additional time to recover (Litvak et al., 2007).

A similar design has been implemented by Iramina and Maeno (2003), but an attenuator was inserted between the first and the second amplifier and before the switch that sets the signal during the pulse to zero. The output of the second amplifier was filtered (high pass and anti-aliasing) before the sample-and-hold circuit. The amplifiers were turned off 10 ms before TMS and turned on 1 ms after. Artifact-free EEG signals could be measured 5 ms after the TMS pulse.

Low slew-rate amplifiers

Another solution for preventing amplifier saturation is to use a simple amplifier/attenuator module that can be inserted between the recording electrodes and any conventional EEG recording device (Thut et al., 2003; 2005; Ives et al., 2006). The module consists of a low slew rate operational amplifier (0.07 V/ μs) with a relatively low-gain bandwidth product (200 kHz). By adjusting the gain to 2200 (downstream complimentary attenuation of 2200 is incorporated in the demultiplexing unit), the high frequency cutoff is equal to 90 Hz, preventing the circuit from responding to the very high slew-rate of the TMS pulse. The slew rate limiting properties prevent amplifier blocking and significantly reduce the artifact, while

most biological signals of interest (up to 90Hz, i.e. the mid gamma range) are still captured. Note that although only frequencies up to 90 Hz are recorded, this contrasts with using low pass filters which modify the data and can induce artifacts themselves (i.e. filter artifacts) in the presence of the high-frequency, spike-shapes TMS-artifact (Ives et al. 2006; the cutoff frequency was 70 Hz in Thut et al., 2003; 2005, see also Epstein, 1995).

The advantage of this method is the simplification of the setup. Also, it can be used as an add-on with any EEG instrument (Ives et al., 2006). Furthermore, this method allows for a continuous registration of the signal. Uncorrected artifact durations were initially reported to be in the order of 200-300 ms (reducible to 5-10ms with post-processing, Thut et al., 2005, see also 3.4.2) and were later reduced to 30 ms at 100% of stimulator output in the electrode directly under the coil (Ives et al., 2006). In some electrodes located further than 5 cm from the coil, there was virtually no artifact (Ives et al., 2006).

Other amplifiers

More recently, additional types of amplifier-circuits have become commercially available which allow for continuous recording without the need for clamping the signal received by the amplifier (although this option remains available with many of these systems). In such systems, the artifact is entirely recorded. A high acquisition rate is recommended such that artifacts can be accurately modeled to allow for its elimination during post-processing (if required).

One option is to prevent amplifier saturation by using modern direct current (DC) amplifiers with wide dynamic ranges that do not contain an initial capacitor subject to saturation by the TMS pulse (Bonato et al., 2006; Fuggetta et al., 2006; Fitzgerald et al., 2009; Taylor et al., 2010). In such systems, the artifact lasts about 30 ms. Another system with wide dynamic range has been used by Levit-Binnun et al. (2010). The first 10 ms had to be removed from the data and artifacts were present up to 50 ms post-TMS, increasing the need to use offline artifact removal procedure.

Another option is to use amplifiers and electrodes designed to work inside magnetic resonance (MR) scanners. These systems have been successfully used with TMS (Fuggetta et al., 2005; Morbidi et al., 2007; Brignani et al., 2008; Veniero et al., 2009; Thut et al., 2011a). In a study by Fuggetta et al. (2005), the MR-compatible amplifiers saturated at approximately 15 ms and recovered during the next 5 ms. The artifact thus remained large during the initial 20 ms, but data could be recorded from 30 ms post-TMS onwards (see Fig. 2). In addition, adjustment of the amplifier sensitivity and operational range may aid in minimizing the TMS artifact (Brignani et al., 2008; Veniero et al., 2009). Selecting high sensitivity (0.1 μ V or 0.5 μ V) over a large range (\pm 3.277 mV or \pm 16.385 mV, respectively) is effective with regards to rapid signal recovery (Veniero et al., 2009). When stimulating a phantom (melon) or non-

brain tissue (knee), Veniero et al. (2009) showed that the signal returned to baseline at about 5-5.6 ms after the TMS pulse. With cortical stimulation, additional peaks occurred at 5.8 and 8 ms; which were interpreted to reflect the earliest recordable cortical responses following EEG contamination by the artifacts (see Fig. 2).

3.1.3 Synchronization boxes

It may be advantageous to gate the signal for TMS discharge to the clock of the EEG data acquisition system, thereby allowing the recording of TMS artifacts without aliasing problems. Such a synchronization box, connected to the EEG unit, has only been used so far by Thut et al. (2003; 2005). As a consequence, TMS pulses and induced artifacts were perfectly synchronized to the sampling rate of the EEG device. At low sampling rate (200 Hz) such as used by Thut et al. (2003; 2005), it is essential to avoid aliasing (variable artifact reconstruction due to under-sampling), especially if template artifacts need to be calculated for subtraction purposes (see part 3.4.2). With higher sampling rates, this gating might not be necessary, but no research comparing artifact reduction with and without such synchronization has been conducted so far.

3.2. The day of the experiment: experimental setup and subject preparation

The choice of suitable hardware should be supported by careful experimental setup and participant preparation. This will help to further reduce or at least monitor the electric and the physiological artifacts (muscle activity, eye blinks/movements, somatosensory and auditory evoked potentials). It can also help to minimize several sources of artifact, such as electrode movement and TMS-induced electric charges.

3.2.1. Electrodes and skin preparation

In addition to having optimal properties to prevent overheating, electrodes should conserve good contact with the skin and impedance should be kept as low as possible (generally below 5 k Ω). Comparing recovery-times and amplitudes of TMS-artifact under high impedance (21-25 k Ω) and low impedance conditions (< 3 k Ω) (stimulation of knee), Veniero et al. (2009) found differences of a factor of 2-3 between the two conditions (recovery-time at 15-20 ms versus 6 ms; amplitude-differences more than doubled in electrodes not directly stimulated).

To achieve low electrode impedance, the skin at the electrode-skin contact has to be cleaned using conventional skin preparation (scrubbing with alcohol and a wooden stick with a cotton tip before applying electrode paste; Ilmoniemi and Kicic, 2010). This will efficiently reduce the impedance in the outer epithelial layers of the skin. However, deeper layers of the skin epithelium will remain intact. Their capacitive properties will lead to a charging of the skin

after the TMS pulse resulting in a slow after-discharge that will contribute to the long-lasting TMS artifact (Julkunen et al., 2008b). In order to reduce the skin capacitance and resistance, Julkunen et al. (2008b) proposed to short-circuit the epithelial layers via a mini-puncturing technique. In their study, the skin at electrode contact was punctured using holes within the electrodes (four per electrode). A custom-made mini-puncturing instrument was used. The optimal length of the tip (i.e. penetration depth) was not separately studied, but the authors recommended a length of about 0.5 mm. An adequate mini-puncture should not cause any bleeding. If applied correctly, mini-puncturing may even cause less discomfort and less skin damage than rubbing (Julkunen et al., 2008b). However, EEG caps should go through disinfection, and the mini-puncture tools should be made from disposable components (Julkunen et al., 2008b).

In comparison to the traditional rubbing procedure, the mini-puncture preparation led to a similar spatial spreading of the artifact, but artifact amplitude and recovery-time were significantly reduced. Twenty-one ms post-TMS, the difference in the size of the artifact between the two preparation techniques was larger than twice the pre-stimulus standard deviation ($2 \times 1.35 \mu\text{V}$). This difference increased with increasing TMS intensity (Julkunen et al., 2008b).

The mini-puncture technique was tested with a biphasic stimulator. With a monophasic stimulator, the problem of accumulated charge is worse, so the recording should benefit even more from the mini-puncturing (Julkunen et al., 2008b).

3.2.2. Wire and Coil placement

It is of primary importance to avoid any contact between the coil and the electrodes to minimize electrode movements (Ilmoniemi and Kicic, 2010). In addition, whenever possible, reorientation of the coil (coil rotation) should be considered in order to keep peripheral muscle activation as low as possible and minimize muscle artifacts, especially when stimulating a frontal or temporal area where muscle artifacts can be considerable (Ilmoniemi and Karhu, 2008). Once coil position and orientation have been determined, reorientation of the wires can help to further reduce artifacts, as discussed below.

The artifact can be reduced in duration if the electrode wires are kept loop free and arranged in a radial way from the center of the magnetic field (Veniero et al., 2009). When recordings are performed with high density EEG, it is recommended that the loose part of the electrode wires are grouped together toward the amplifier and oriented away from the coil cable to avoid additional interference (Veniero et al., 2009).

Sekiguchi et al. (2010) have modeled and systematically studied the effects of electrode wire positioning on artifact size. It was argued that one can create a configuration (electrode wire

perpendicular to the coil handle) in which the currents, running in opposite direction in the two rings of a figure-of-eight coil, should counteract each other. In a circuit model with one recording electrode and a reference electrode stimulated by a figure-of-eight coil, this supposition proved accurate. Over a human scalp, the real artifact was considerably reduced by arranging the wires perpendicular to the coil handle, although it could not be totally eliminated (Sekiguchi et al. 2010). To optimize artifact reduction, Sekiguchi et al. (2010) proposed a stepwise procedure of wire arrangement consisting of recording TMS-induced artifacts, then rearranging the wires for artifact-contaminated channels.

3.2.3. Controlling TMS boosters

The TMS recharge artifact can be controlled at the TMS device. By controlling the power supply unit and using only one booster to recharge the TMS circuit (e.g. in Magstim Super Rapid), it is possible to delay recharge and associated artifacts to periods of less physiological interest (Veniero et al. 2009). The alternative of inserting a recharging delay circuit in the stimulation device could be used to the same effect (Veniero et al. 2009). If this is not possible, the artifact can be dealt with by post-processing (in particular 3.4.1), as it is of short duration and low amplitude.

3.2.4. Sound masking

Several studies have pointed to the problem of contaminations by the auditory response to the coil click (e.g. Nikouline et al., 1999, Paus et al., 2001; Fuggetta et al., 2005; Massimini et al., 2005; 2007; Ferrarelli et al., 2008; Rosanova et al., 2009). In this regard, it is important to note that the coil click can be conducted not only by air but also by bone (vibration of the temporal bone), bypassing the middle ear and reaching the cochlea directly. Nikouline et al. (1999) recorded the auditory potentials created by the coil-click (100 dB at 0.5 cm from the coil) under three conditions. In the first, the center of the coil was held 2 cm above the scalp over the left motor cortex. In the second, the coil was held at the same position, but with a plastic piece rigidly connecting the head and the coil. In the last condition, normal stimulation was performed with the coil pressed against the head. In all 3 cases, the negative-positive (N1-P2) auditory complex was clearly identifiable in the EEG. The average N1-P2 peaks (maximal over central and parieto-temporal regions) were 9, 14, and 23 mV, respectively. To eliminate this artifact, the following procedures have been adopted.

Although simple hearing protection will help to reduce air conduction, it will not be sufficient for its elimination. More effective for masking the coil-generated click is to play a loud 90 dB white noise through insert earphones. Participants have reported that this noise is generally sufficient to mask the auditory input and no auditory-evoked potentials (AEP) have been recorded when the coil is discharging 2 cm above the head under this condition (Paus et al.,

2001; Fuggetta et al., 2005). However, such sound masking may be insufficient to prevent the auditory artifact resulting from bone conductance.

Other studies limited the intensity of the masking noise by designing the noise so that the pressure level at each frequency matched the pressure levels of the time-varying frequencies from the TMS click. The volume was then adjusted until the subject did not perceive any TMS click. Bone conduction was attenuated by placing a thin layer of foam between the coil and the scalp (Massimini et al., 2005; 2007; Ferrarelli et al., 2008; Rosanova et al., 2009). These procedures effectively abolished the auditory stimulation associated with TMS as demonstrated by the absence of any evoked response to sham TMS stimulation (Massimini et al., 2005; Ferrarelli et al., 2008).

3.2.5. Avoiding orienting to TMS

In addition to auditory and tactile sensory brain responses, TMS may induce cognitive EEG components, e.g. such as those associated with attentional orientation towards TMS. In order to avoid such orienting effects, participants might be asked to participate in a distracting task. In a study from Huber et al. (2008), subjects were engaged in a simple oddball task. Interspersed within a noise mask, tones were played at irregular interval and the participants had to respond as fast as possible with a mouse button click each time a tone was played. However, in many experimental designs, such distracting tasks might be a problem as reactivity and connectivity depend on current brain state and therefore also on mental activity (Miniussi and Thut, 2010).

3.2.6. Further control conditions

In some experimental designs (and when artifacts cannot be avoided), one might benefit from including control conditions to characterize some of the physiological artifacts: such as the residual auditory-evoked potentials and tactile-evoked potential created by the vibration of the coil during coil discharge. Modeling these artifacts can help to tease apart which components of the TMS-induced potentials reflects a genuine TMS effect and which are un-specific, i.e. due to the associated sounds and coil taps. These artifacts can then be eliminated through subtraction. To model these artifacts, a sham condition (Fuggetta et al., 2008) or real stimulation in the absence of the tested task (Thut et al., 2003; 2005; Fuggetta et al., 2006) have been used, the latter additionally emulating the electrical artifacts that can then also be subtracted (see section 3.4). Finally, assessing TMS effects as a function of changing coil orientation relative to the most effective stimulation position (perpendicular to the underlying gyral folding pattern, Thielscher et al., 2011) might also help to differentiate which components are specific to the optimal orientation (and therefore reflect genuine TMS-evoked brain responses) and which are not (Bonato et al., 2006; Thut et al., 2011a).

3.2.7. Familiarization with the TMS and EEG setting

If the participants are TMS- and EEG-naïve, it will be advantageous to familiarize the participants with the particular setting by running training sessions, especially for TMS. It is important that the participant feel comfortable with the procedure, which will help to reduce eye movements, blinks, and muscle contraction. It will also likely reduce startle and orienting towards TMS.

3.2.8. EOG

It is recommended eye movements and blinks be recorded to determine and discard contaminated trials off-line. TMS artifacts render automatic artifact detection or ocular correction procedures difficult (Bender et al., 2005), but oculomotor artifacts can still be rejected by visual inspection.

3.3. During the recordings

For some of the artifact reduction procedures (see post-processing below), it is important to obtain reproducible artifacts (besides reproducible signals). Reproducible artifacts are crucial for the calculation of a reliable artifact template that can then be subtracted from the data. Additionally,, reproducible artifacts are easier to localize via topographical maps (see section 3.4). To obtain reproducible artifacts, the positioning of the coil relative to EEG-hardware should be kept as constant as possible. A movement as small as 5 mm might cause large changes in artifact morphology (in addition to large changes in brain response) (Komssi et al., 2002 - see below). Further, any coil displacement might increase the risk of displacing an electrode. Coil movements might be prevented by the use of a coil holder or by MRI-guided neuronavigation, both of which allow for precise and stable coil placement and orientation.

For the same reason, wire orientation, TMS intensity, EEG impedances, etc. should be kept as stable as possible. For longer experiments (>30 min), the impedances should be checked regularly to avoid size increase as the electrode paste dries (Litvak et al., 2007).

3.4. After the experiment: post-processing

Even when all the above steps are meticulously followed, TMS-EEG artifacts are unlikely to be eliminated completely. For instance, even with sample-and-hold circuits to fully prevent any brief peak-activity from entering into the amplifier during the hold-interval, there is likely some induced charge that does not decay completely before the end of the hold-period. This can result in residual (but significant) EEG contaminations (Litvak, 2007), which

requires post-processing. To remove residual artifacts, several offline analysis approaches have been designed which, presumably, do not distort the physiological signal.

It has to be highlighted here that any removal of TMS-induced artifact comes at the risk of removing TMS-induced brain signals. We therefore recommend that post-processing for artifact removal only be used if un-avoidable and that special care be taken if the corrected artifact stretches into the time-window of interest where EEG-measurements are interpreted (often after 15ms post-TMS).

3.4.1. Removing the channels or period containing the TMS artifacts

The first possible way to deal with the artifacts is to simply exclude the channels contaminated by systematic artifacts (Kahkonen et al., 2001; 2005; Komssi et al., 2004). Unfortunately, the most contaminated channels are usually those closest to the stimulation site, which also contain the most information regarding brain reactivity to TMS. In addition, in the case of source reconstruction, such removals introduce bias in source localization (Litvak et al., 2007). Given that late signal recovery is not only channel-dependent but also varies across trials, rejecting the most affected trials in a channel-specific way might still conserve an acceptable number of trials per channel for subsequent analysis (Reichenbach et al., 2011).

Another possibility is to simply ignore the initial tens of milliseconds containing the main part of the artifact and analyze later evoked responses. Usually, TMS-EEG analysis starts 6 to 40 ms after the pulse, coincident with the onset of many signals of interest (Fuggetta et al., 2005; 2006; Esser et al., 2006; Brignani et al., 2008; Fitzgerald et al., 2009, Veniero et al., 2009; Thut et al., 2011a). In order to also eliminate characteristic auditory and sensory responses, the analysis could focus on a very restricted period of time (e.g. from 20 to 50 ms after the pulse), if this is the period of interest (Kahkonen et al., 2001).

After the removal of data from the artifact period, it is possible to reconstruct a continuous data set (however, without any meaningful information in the discarded section). For instance, Fuggetta et al. (2006) cut out 40 ms segments (from -2 ms to 38 ms) and joined data points from before and after each removed segment. The random voltage step between the joined data points of each single trial was eliminated via trial-averaging. In a study on brain oscillations, Fuggetta et al. (2008) concatenated artifact-free periods extracted from an rTMS session. This created edge artifacts in the EEG data at the junction between the segments. The frequency bands around the frequency of the edge and their harmonics did not reflect brain oscillations, but any intermediate frequency band was reliable (Fuggetta et al., 2008). When the first tens of milliseconds post-TMS are eliminated, another possibility is to set all values to zero (zeropadding, see e.g. Van Der Werf and Paus, 2006; Esser et al., 2006; Huber et al.,

2008) or to interpolate the missing data by third order polynomial curves followed by appropriate filtering (Reichenbach et al., 2011).

Thus, for many studies, simply discarding channels, trials, or periods of time containing the artifact might be sufficient, particularly if artifact durations are short (<10ms). Information concerning the local early response to the TMS pulse might consequently be lost.

3.4.2. Creating TMS template artifacts and subtraction

In order to ensure that a TMS-evoked component is not reflective of an artifact, it might be useful to compare EEG responses obtained from scalp electrodes with those recorded from a phantom head (e.g. Bender et al., 2005; Veniero et al., 2009; Thut et al., 2011a). Bender et al. (2005) compared the N100, a negative component around 100 ms post-TMS (supposed to reflect inhibitory processes - Nikulin et al, 2003) to the TMS-evoked potential that was produced in the same time window when a glass dummy head was stimulated (this head was covered by a cloth soaked with water, so that impedances of about 5 k Ω were obtained). The short, sharp EEG artifact produced by the TMS pulse was transformed by the amplifier's hardware and filter characteristics to a slightly delayed high-frequency oscillation with decreasing amplitude. Even though this artifact was still present 100 ms after the pulse, the N100 recorded in children was significantly larger ($-130.6 \pm 71.9 \mu\text{V}$) than the "N100" recorded in the dummy ($4.8 \pm 0.9 \mu\text{V}$), supporting a neuronal origin of the N100.

While TMS-EEG on a phantom head elicits purely electrical artifacts, others have created a template of the artifact by recording EEG during TMS at rest (Thut et al., 2003; 2005; Ives et al., 2006; Reichenbach et al., 2011). Obtained through multichannel recordings for each subject, this template can then be used to isolate the neuronal signal from artifact by subtraction (experimental condition minus rest). In these studies, participants were performing a task, and the purpose was to explore the changes to task-related activity as a consequence of TMS (not the activity evoked by the TMS pulse per se). By subtraction of the template artifacts, one will not only subtract artifacts, but also neuronal activity that has been induced by the TMS pulse in the brain tissue underlying the coil, isolating task-related potentials (TMS-modified or unaffected) from any TMS-locked event.

Thut et al. (2003; 2005) tested this procedure using a visual task, applying TMS over the occipital pole and recording visual evoked potentials (VEPs) (using low slew-rate EEG amplifiers). The template artifact calculated in a TMS only condition (rest) lasted up to 200-300 ms. Despite this considerable contamination, VEPs could be retrieved by subtracting the template artifact (TMS only) from the experimental condition (visual stimulation + TMS). The VEPs resulting from subtraction were virtually identical to control VEPs (recorded during a visual task without TMS) when TMS was applied at visual stimulus onset (see Fig. 6), but were modified by TMS (in P1- and N1-amplitude) when applied around 100 ms after

visual stimulus onset (i.e. at the moment of most consistent visual suppression). Using a similar procedure, Reichenbach et al. (2011) found a supra-additive interference between occipital TMS- and VEPs (P1 for 6 over 7 subjects and N1 for the last subject) dependent upon TMS-intensity. Subtraction methodology was also applied with TMS to other areas, e.g. posterior parietal cortex and vertex (Fuggetta et al., 2006) and the cerebellum (Thut et al., 2005).

The advantage of subtracting TMS-artifact templates is that it deals with both electrical artifacts and auditory/somatosensory contaminations (although at the expense of eliminating TMS-induced activity that is of interest in many applications). Subtraction of template artifacts is therefore useful for studying single-pulse TMS interference with the generation of functional, task-related signals (e.g. event-related potentials) or with spontaneously generated (patho-) physiological activity (e.g. epileptic spikes). In exchange, it does not allow for the study of brain reactivity and connectivity because TMS-induced activity, which is confounded in the artifact, is also subtracted (Thut et al., 2005).

3.4.3. Source analysis with PCA around TMS administration

This artifact correction option proposed by Litvak et al. (2007) is based on a method for correcting eye-movement artifacts using scalp topographies and source analysis (Berg and Scherg, 1994). It is implemented in the BESA software and also available with the open-source MEEGTools toolbox (SPM8).

The main feature of this algorithm is that it models artifact topography and brain signals separately, which allows for disentanglement despite spatial and temporal correlation. To model the artifact, a principal component analysis (PCA) is performed during the time period in which the artifacts dominate (typically the first 15 ms after the pulse for the immediate TMS artifact). PCA is a linear transformation, from the original EEG data collected in channels to data expressed in an orthogonal coordinate system, in which the greatest variance is accounted for by the first component, the next largest variance by the second, etc. Thus, the first few components of the PCA should reflect the major part of the artifact. To model the brain signals, a surrogate model of the brain containing 15 sources is used, capable of reasonably approximating activity generated in the cerebral cortex (Scherg et al., 2002). A general model of brain activity (using the surrogate model) and artifacts (entering the first PCA component) is used to calculate, from the original EEG signals, the activity of both brain and artifact sources. Performing the inverse calculation - after removal of the artifact source - leads to cleaner EEG signals. Further PCA artifact components are then added one by one to the general model until no artifact can be seen in the EEG signals. Using the resulting artifact-corrected data set (single subject data) and based on the grand-mean averaged data, a better source model accounting for brain response to TMS is then built

(grand-mean model). The artifact correction procedure outlined above is then repeated on single subject data, with the grand-mean based model replacing the surrogate model. For an illustration of the outcome of this algorithm see Fig. 6.

Litvak et al. (2007) applied this artifact correction procedure to retrieve early TMS-evoked activity (10-60 ms latency) which was contaminated with residual artifacts despite the use of TMS-EEG dedicated hardware. Later parts of TMS-evoked responses were not affected. The results revealed multiple source activity already in this early phase of TMS-evoked responses.

Although the application of the method was first shown with EEG signals recorded with a dedicated sample-and-hold system (Litvak et al., 2007), it is also applicable with standard EEG systems so long as saturation is prevented (Levit-Binnun et al., 2010).

3.4.4. ICA approach

Independent component analysis (ICA) has been proposed for TMS-artifact removal by Hamidi et al. (2010) (on data recorded through a sample-and-hold system). Decomposing EEG data by ICA involves a linear transformation from data collected in channels to data expressed in “virtual channels” (components). The independent components are chosen to produce the maximally independent signals (in the time domain). Because each EEG electrode records a linear combination of activity from distinct (physiological or artifactual) sources, the ICA procedure should ideally allow for the isolation of these sources of activity.

As with other procedures, the difficulty lies with distinguishing between artifactual ICA-components and physiological ICA-components (and to identify potential mixing). To this end, the artifact detection and removal procedure proposed by Hamidi et al. (2010) relies on three main principles of artifact characteristics: first, the artifacts should fulfill the criteria of being spatially localized. In contrast to physiological EEG signals that will be detected by many electrodes on the scalp due to volume conductance (even from a very localized source), TMS-related artifacts originating from outside the skull are recorded mainly in the electrodes closest to the TMS coil. Second, TMS artifacts should fulfill the criteria of being temporally predictable, occurring systematically at pulse onset and lasting only for 10-15 ms after the pulse. Third, during repeated application of TMS at a fixed frequency (repetitive TMS, as in Hamidi et al. 2010), the power spectra of artifact components should clearly be of a non-physiological nature. The artifact component has a strong peak at the stimulation frequency and several harmonics superimposed on a flat power spectrum. Any physiological signal, on the other hand, should cover a wider band-width, not contain strong harmonics, and maintain a $1/f$ pattern in the power spectrum.

For artifact-identification and reduction, Hamidi et al (2010) applied ICAs at two stages of pre-processing (first on continuous EEG data and then on epoch data). To make sure that only ICA-components reflecting artifacts are discarded, Hamidi et al. recommend to inspect the data for mixed components (showing elements of both physiological data and the above artifact criteria). In the case of mixed components, only those that explain relatively little variance in the data should be eliminated. As a final step, comparing the results with or without these ambiguous components might help to further validate the identification of artifact components (Hamidi et al., 2010). Using this method, Hamidi et al. (2010) studied the evolution of TMS-evoked activity over the course of a 10 Hz train of multiple successive pulses. The amplitude of evoked activity within each inter-pulse-interval (100 ms) followed a quadratic relationship with pulse number, revealing complex dynamics of neuronal recruitment over an rTMS train.

It should also be noted that the ICA procedure outlined above partially relies on the TMS pulses being applied regularly and stimulation conditions remaining constant during the experiment.

3.4.5. Filtering methods

It is not advisable to use conventional filters during recording or upon uncorrected (artifact-contaminated) signals as these might interact with the residual artifact and produce ringing artifacts (especially when low pass filters are applied) thereby increasing artifact duration (e.g. Taylor et al. 2008). In addition, despite the fact that low frequencies usually reflect physiological signals and high frequencies usually reflect artifact, the large overlap between spectral components prevents any simple filter from removing the artifact without distorting the physiological signal (Morbidi et al., 2007). To remedy this, specific offline filter strategies have been tested.

Morbidi et al. (2007) contrasted different filtering methods aimed at removing the electrical artifact from a recorded signal (data recorded with an MR-compatible EEG system). Of the two filter strategies tested (Wiener filter versus Kalman filter), the Kalman filter approach (working properly on a non-stationary signal) yielded better results and is summarized below.

If one assumes that the electrophysiological signal is a stationary, zero-mean signal, then it is possible to obtain the average artifact by averaging the signal (electrophysiological plus artifact) over several trials. The average of the artifact can then be subtracted from individual trials in order to obtain the individual physiological signal. However, the artifactual signal is not necessarily perfectly reproducible and might contain a stochastic portion, thus preventing perfect results by simple subtraction. The Kalman filter does not rely on artifacts and signal being jointly stationary. Two dynamic models describing EEG and TMS signal generation are established and the Kalman filter is applied to their linear combination. The Kalman filter

is a recursive (two-step) method. In the first step, the signal at time t can be estimated through the model from the estimate signal at the time $t-1$. The uncertainty relative to “real data” is estimated through the variance given to the model. In the second step, the estimation is corrected by averaging the previously estimated signal and measured signal, with weights dependent upon the uncertainty of the model.

For an example of Kalman filtering taken from Morbidi et al. (2007) see Fig. 6.

3.4.6. Source reconstruction to identify artifacts

In order to remove artifact from electrical contamination, Huber et al. (2008) used a source reconstruction method. The origin of the average electrical activity of each peak of the TMS-evoked response was localized. A failure to locate a source within the brain was considered as an evidence for artifactual contamination.

3.4.7. Modeling artifacts by exponential functions

Artifacts can take the form of an initial, steep amplitude increase (offset) followed by a slow exponential decrease. This slow decay likely reflects the slow discharge of accumulated charges during the pulse and can be fitted with exponential functions (Litvak et al., 2007) for removal from the data.

3.4.8. Final automatic rejection (after the major portion of the artifact has been deleted)

After the main electrical artifacts have been removed, traditional algorithms can be applied to remove residual TMS, muscle, or EOG artifacts. Two criteria are generally used: amplitude of the signal and slope (first derivative) which should both be kept below chosen thresholds (Litvak et al., 2007; Fuggetta et al., 2008).

4 Benefits from combining TMS and EEG

To illustrate the scope of this unique method combination, we outline some of its applications below.

4.1. Systems and cognitive neuroscience

In the fields of systems and cognitive neuroscience, the combination of TMS and EEG has opened new ways to study brain connectivity and function. Our overview of some key findings in these fields is organized according to the three main TMS-EEG approaches (as identified in Miniussi and Thut, 2010): (1) the “inductive” approach, during which TMS-

induced brain activity is measured in the absence of any task (see also Komssi and Kahkonen, 2006), (2) the “interactive” approach, during which either TMS-induced modulation of task-related activity, or task-related modulation of TMS-evoked activity is assessed (see also Taylor et al., 2008), and (3) the “rhythmic” approach, during which TMS-EEG interactions are studied within the perspective of brain rhythms (see also Thut and Miniussi, 2009).

4.1.1. The inductive approach

TMS can be used independently (without EEG) to probe the excitability of the primary motor cortex (M1) or the excitability of the visual cortex (V1/V2) via the measuring of TMS-induced motor-evoked potentials (MEPs) from target muscles or via the assessment of TMS-induced illusory visual percepts (phosphenes). Other, “silent” brain areas have also been stimulated without concurrent recordings of brain activity, but with other goals in mind, i.e. to explore the role of the stimulated area in a given task. Through the recording of TMS-evoked potentials (TEP) across the scalp, TMS-EEG can be used to quantify cortical excitability beyond motor and visual areas. By analyzing local brain responses, the excitability of stimulated areas can be probed. In addition, studying the subsequent spread of activity to anatomically connected areas provides information on brain connectivity.

Cortical excitability

TEP-amplitude can be used to quantify local excitability. In doing so, different TEP peaks should be distinguished. Upon stimulation of the motor cortex, evoked activity lasts up to 200 ms post-TMS (Bonato et al., 2006). Successive positive and negative TMS-evoked deflections have been consistently identified over the scalp (e.g. Paus et al., 2001; Komssi et al., 2004; Bonato et al., 2006; Komssi and Kahkonen, 2006; Fitzgerald, 2010). These include peaks usually defined as N15/N18, P30, N40/N45, P55/P60, N100, P180/P190 and N280, which originate from different areas (Paus et al., 2001). While some reflect the activation of the stimulated cortex (N18, N45, P55), others are related to a spreading of activity toward other regions (P30) or to a widespread brain response (N100). The N100-P190 complex was initially associated with the sound emitted by the discharging coil (Nikouline et al., 1999). Recent studies using white-noise sound masking and manipulating coil orientation as controls, and comparing the N100-P190 with AEP- and SEP-topographies, have determined that part of this component is a genuine TMS effect (Bender et al., 2005; Bonato et al., 2006).

To characterize the excitability of the cortex in more detail, the shape of the input-output curve (i.e. stimulus intensity-response curve) has been assessed for different peaks of the EEG-response (Komssi et al., 2004; Kahkonen et al., 2005; Ferrarelli et al., 2008). TEP-amplitudes increase with stimulus intensity, but this relationship depends on the peak examined and the area stimulated. TMS of M1 often evokes measurable brain activity at low

stimulus intensities, probably significantly below 60% motor threshold (MT) (Komssi et al., 2004), whereas the prefrontal cortex shows less excitability (Kahkonen et al., 2005). This provides useful information for fine-tuning of TMS intensity during an experiment or for therapeutic treatment, e.g. for depression. Because the function of motor and prefrontal cortex can be altered by neurological disease, one should be aware that any relation between the excitability of the two areas in healthy subjects cannot be directly transferred to patients (Komssi et al., 2004; Kahkonen et al., 2005).

In addition to defining local excitability via TEPs, the inductive approach can also substitute for MEPs during the study of short or long intracortical inhibition (SICI or LICI) and intracortical facilitation (ICF) via the paired-pulse paradigm (Paus et al., 2001; Daskalakis et al., 2008; Fitzgerald et al., 2009). Briefly, in the paired pulse paradigm, a conditioning motor cortex TMS pulse can either promote or decrease the MEP evoked by a second test pulse, depending upon interpulse interval (IPI) (Claus et al., 1992; Kujirai et al., 1993; Ziemann, 1999). MEPs typically decrease with IPIs of 3-ms or 100-ms (SICI and LICI respectively) and increase with an IPI of 20 ms (ICF). Integration of TMS and EEG allows one to explore ICF and ICI in neural substrates other than M1 (Paus et al., 2001; Daskalakis et al., 2008; Fitzgerald et al., 2009). Daskalakis et al. (2008) showed, for instance, that both within the motor cortex and the prefrontal cortex, the LICI paradigm resulted in significant suppression of mean TMS-evoked brain activity. This suppression was correlated with MEP-suppression across subjects.

Neural connectivity

Examining the time-course of TMS-evoked scalp potentials and their possible neural origin has also contributed to the study of neural connectivity. To date, neural connectivity has been probed using TMS over the cerebellum (e.g. Iramina and Maeno, 2003), the sensori-motor and occipital cortices (e.g. Ilmoniemi et al., 1997), and the motor and posterior parietal cortices (e.g. Iwahashi et al., 2008; Litvak et al., 2007). Spreading of activation across areas ipsilateral to stimulation was recorded within 5-15 ms (Ilmoniemi et al., 1997; Litvak et al., 2007) and across homologous regions in the opposite hemisphere within 20 ms (Ilmoniemi et al., 1997; Iwahashi et al., 2008). Both transcallosal and subcortical pathways might explain this contralateral hemispheric response.

Examining neuronal connectivity as a function of different states of consciousness, namely sleep and wakefulness, has revealed the dynamic nature of neural connectivity (Massimini et al., 2005; 2007). During wakefulness, TMS evoked a low-amplitude wave with a complex, differentiated pattern - including long-range spreading of cortical activity. Contrarily, during sleep, TMS produced either a local slow-wave (after stimulation of the sensorimotor area) or a widespread slow-wave (after stimulation of the premotor area). These findings were

interpreted to be reflective of a sleep-related loss of ability of the thalamocortical system to enter states that are both integrated and differentiated: the system either breaks down into independent modules or bursts into an undifferentiated response (Massimini et al., 2005; 2007). Both features may be important to account for the fading of consciousness during the early phases of sleep (see the integrated information theory of consciousness in Massimini et al., 2009).

Finally, analyzing the spread of activation can also reveal the existence of distinct “functional” connections. For instance, stimulation of the posterior parietal cortex has confirmed the existence of an “attentional” circuit (revealed by co-activation of prefrontal cortex) as well as a connection between dorsal and ventral streams (revealed by co-activation in temporal-occipital regions) (Zanon et al., 2010).

In the absence of any tasks, the functional relevance of changes in excitability and connectivity remain hypothetical. Below, we describe what the TMS-EEG combination has achieved in the study of the “active” brain.

4.1.2. The interactive approach: exploring network dynamics of the active brain

TMS-EEG can provide insight into how TMS acts on the brain to alter behavior. Specifically, it allows one to establish how modifications in brain reactivity and connectivity are reflected at the behavioral level. One approach consists of studying the modification of task-related brain activity (e.g. event-related potentials) by TMS, while another consists of studying the modification of TMS-evoked potentials as a function of task.

Modification of task-related activity by TMS

In tasks requiring the allocation of visual attention, alterations of visual-evoked potentials (VEPs) or of anticipatory visual activity over posterior sites (e.g. alpha-activity) have been described after stimulation of remote areas, namely the right parietal cortex (Fuggetta et al., 2006; Capotosto et al., 2009), and the frontal eye field (Taylor et al., 2007a, Capotosto et al., 2009). These alterations were absent after stimulation of control sites. The study by Fuggetta et al. (2006) targeting parietal cortex showed impairment in task performance associated with a VEP-change, causally linking the parietal cortex with attentional control mechanisms. Likewise, the EP-findings of Taylor et al. (2007a) highlight the causal role of the frontal eye field (FEF) in the attention-mediated regulation of brain activity evoked over posterior sites. The findings of Capotosto et al. (2009) revealed a causal role of FEF and of parietal cortex but in the control of on-going posterior (alpha) activity (recorded during attention orienting in anticipation of a forthcoming visual event). All these studies therefore reveal cortico-cortical interaction in the regulation of input control.

Modification of TMS-probed excitability and connectivity by task

Because the amplitude and configuration of the TMS-evoked response depends on vigilance states (Massimini et al., 2005; 2007), TMS-EEG also offers a new opportunity to explore brain reactivity and effective connectivity in the active brain during different tasks or stages of task performance.

Task-dependent changes in brain reactivity were illustrated by Bender et al. (2005), who showed that the amplitude of the N100 potentials evoked by motor cortex TMS is reduced during motor preparation when participants anticipate a forthcoming stimulus prompting a manual response. Because this involved pre-activation of the cortical structures necessary for a fast response, the attenuation of the TMS-evoked N100 indicates that this component may reflect an inhibitory response to the sudden, TMS-induced synchronization of neuronal discharge (Bender et al., 2005). The link between inhibitory processes and the N100 was later confirmed by studies in which participants were asked either to resist or assist TMS-induced movements (Bonnard et al., 2009) or mechanically-induced movements (Spieser et al., 2010). In both instances, subjects were able to intentionally modulate their motor response to the external stimulus. EEG recordings revealed decreased N100 amplitude during preparation to assist as compared to resist, suggesting anticipatory reduction of intracortical inhibitory processes (Bonnard et al., 2009; Spieser et al., 2010).

Task-dependent change in effective connectivity was illustrated by Taylor et al. (2007b) who showed that TMS of the medial frontal cortex (close to the area usually described as the pre-supplementary motor area) impaired behavioral and EEG-measures of motor preparation, the latter reflected in changes of activity over M1 (remote effect). Notably, these effects were only observed when a conflict should be resolved, but TMS had no effect in the absence of conflict.

These studies underscore how different tasks can shape the balance between excitation and inhibition, or functional connectivity between anatomically connected areas.

4.1.3. The rhythmic approach

TMS-EEG combination has also been used to elucidate the role of brain oscillations in brain function. Here, again, TMS-EEG can be used in two ways: the first consists of studying the modification of on-going brain oscillations by TMS, while the second consists of studying the modification of TMS outcome measures (excitability and connectivity) as a function of background oscillatory activity.

TMS-influences on rhythmic brain activity

In addition to analyzing TMS-induced potentials in terms of components (or peaks), responses can be analyzed in terms of spectral composition. Single pulses over the motor cortex lead to synchronization in the α - and/or β -bands (Paus et al., 2001; Fuggetta et al.,

2005) as well as enhanced coherence between motor and fronto-central areas, mainly in the α band (Fuggetta et al., 2005). It was suggested that either the pulse had activated “idling neurons” that, in turn, began to oscillate at α - and/or β -frequencies, or more likely, that the pulse led to a phase-reset of ongoing spontaneous activity in a population of neurons (Paus et al., 2001; Fuggetta et al., 2005). Such phase-resetting of ongoing oscillations might be established in cortical networks (local pacemaker). However, the recruitment of a thalamic pacemaker through thalamocortical interactions is also conceivable (Fuggetta et al., 2005; Van der Werf et al., 2006). The phase-resetting hypothesis was supported by Van der Werf and Paus (2006) who studied phase-locking of single-trial beta-responses over motor cortex. This phase-locking was highly significant, whereas the amplitude modulation was not. It is noteworthy that, while TMS is an external and artificial event, the oscillations induced by TMS are likely of physiological origin. Rosanova et al. (2009) showed that when stimulated, each region tended to preserve its own natural frequency (e.g. α -oscillations over occipital cortex, β over parietal and fast β/γ -oscillations over frontal areas). Hence, single-pulse TMS reveals the “natural rhythms” of different regions.

An interesting corollary of inducing brain oscillation by a single pulse is the prospect of entrainment when further TMS pulses are applied in phase-alignment with the induced oscillation. For instance, when stimulating an area oscillating spontaneously at α (i.e. an α -generator), one would expect to induce an α -oscillation by one TMS pulse (Rosanova et al., 2009) and to further enhance (entrain) such an oscillation with further TMS pulses applied at α -frequency in phase with the induced oscillation. The hypothesis that entrainment of physiological rhythms with frequency-tuned rhythmic TMS is feasible has been supported by TMS of an α -generator at α -frequency and concurrent EEG recordings (Thut et al., 2011a). Note that these entrainment effects have been measured during application of only a few pulses (5 pulse TMS-trains in Thut et al., 2011b) and corroborate earlier studies inferring entrainment of brain oscillations by short rhythmic TMS trains from mainly behavioral measures (Klimesch et al., 2003; Romei et al., 2010, 2011; Sauseng et al. 2009). For instance, Klimesch et al. (2003), who introduced the idea of entraining brain oscillations at the frequency of stimulation, showed that parietal TMS tuned to the individual α -frequency benefited mental rotation while stimulation at other frequencies had no effect. This finding is in accord with EEG-findings that high posterior α -power predicts good performance in mental rotation tasks. More recently, frequency-specific behavioral effects of rhythmic TMS have been reported after parietal stimulation for performance in location-based and feature-based attention tasks as well as working memory tasks (Romei et al., 2010, 2011; Sauseng et al. 2009).

Other modifications of spectral content have been reported after prolonged rTMS (usually >5 minutes of stimulation). Various rTMS-parameters, such as duration of stimulation,

frequency, and intensity, will influence the local oscillatory activity as well as synchronization between different areas (Fuggetta et al., 2008; Brignani et al., 2008). For instance, trains of 5 Hz rTMS that increase cortical excitability as reflected in enhanced MEP amplitude have been associated with a decrease of coupling between brain areas, possibly reflecting reduced efficacy of inhibitory cortico-cortical and/or cortico-subcortico-cortical projections (Fuggetta et al., 2008). On the contrary, 1 Hz rTMS promoting cortical inhibitory mechanisms as reflected in a decrease in MEPs amplitude translates into a local increase of power in the α -band (Brignani et al., 2008). But, see Veniero et al. (2011) for changes in brain oscillations that are independent of rTMS-protocol (e.g. 5 Hz vs 1 Hz). As this chapter is focused on EEG signals recorded during TMS, any reader interested in EEG aftereffects of rTMS is invited to refer to the review by Thut and Pascual-Leone (2010).

Rhythmic background EEG activity influencing TMS-outcomes

When stimulating motor cortex with constant parameters, variability of TMS outcome (MEP-amplitude) can be attributed to variability in the excitability of the spinal motoneuron pool recruited by the cortical efferent volley induced by TMS. In accordance with this view, MEP-amplitude is only inconsistently or weakly correlated with the amplitude of TMS-evoked potentials, such as the N100 amplitude (Paus et al., 2001, but see Bender et al., 2005), the peak-to-peak amplitude of the N15-P30 complex (Maki and Ilmoniemi, 2010a), or the integrated activity of the TMS-evoked response at electrodes over motor, premotor and sensorimotor cortices (Huber et al., 2008). In other words, variability in MEP-amplitude is only weakly related to variability in cortical responses to TMS. From this, it stands to reason that an important source of MEP variability is subcortical. However, variability in TMS outcomes may also be related to spontaneous fluctuations in on-going oscillatory activity.

Romei et al. (2008a; 2008b) showed that subsecond fluctuations in α -band power at occipital electrodes just prior to stimulation of occipital cortex were significantly linked to the presence or absence of an illusory visual percept (phosphene), both within and across individuals. These spontaneous fluctuations in brain excitability could be functionally relevant: the brain possibly maximizes the prospective gathering of visual information by periodically changing sensitivity for a given location (Romei et al. 2008a). Similarly, power in the alpha-, beta- and/or gamma-bands just before stimulation of M1 has been shown to correlate with MEP-amplitude (Zarkowski et al., 2006; Lepage et al., 2008; Sauseng et al., 2009; Maki and Ilmoniemi, 2010b). Finally, the phase of spontaneous oscillation also plays a role in shaping TMS-probed cortical excitability (Maki and Ilmoniemi, 2010b; Dugué et al., 2011).

4.2. Clinical applications

A growing understanding of the normal brain constitutes a basis for the development of new clinical tools, both in diagnosis and treatment. For instance, the dependence of brain response on TMS intensity (Komssi et al., 2004) or the triggering of natural oscillations in response to stimulation of different areas (Rosanova et al., 2009) may have diagnostic potential for several pathologies such as depression, epilepsy, or disorders of consciousness (Ilmoniemi and Kicic, 2010). Similarly, TMS-EEG may provide a window into cortical connectivity, which could be useful for prognosis, for instance following brain injuries (Komssi and Kahkonen, 2006). Regarding treatment, studies on sleep (Massimini et al., 2005; 2007; Huber et al., 2008) have opened new perspectives for increasing sleep efficiency (Massimini et al., 2009). Similarly, the possibility to entrain brain rhythms (Klimesch et al., 2003; Thut et al., 2011a; 2011b) and concurrently modify cognitive performance (Klimesch et al., 2003, Romei et al., 2010, 2011; Sauseng et al. 2009) or promote synchronized oscillations in two areas by applying synchronous bifocal stimulation (Plewnia et al., 2008) might be further exploited for the treatment of various cognitive deficits. Below, we review some TMS-EEG studies on the understanding, diagnosis, and treatment of neurological conditions.

4.2.1. Pathophysiology

The TMS-EEG combination has been used to explore abnormalities in brain reactivity and connectivity in several conditions.

Alcohol intoxication modifies connectivity (Kahkonen et al., 2001) as well as reactivity of the prefrontal cortex (Kahkonen et al., 2003). These changes may be linked to an interaction of alcohol with a large variety of inhibitory and excitatory mechanisms and may be associated with symptoms of alcohol intoxication such as mood lability and impairments in attention, memory, and judgment (Kahkonen et al., 2003).

Abnormalities could also be reflected in the spectral content of brain response to TMS. In schizophrenia patients, for instance, TMS-evoked γ -activity and the spreading of γ -oscillations are impaired over motor, premotor, and prefrontal cortices (Ferrarelli et al., 2008; Farzan et al., 2010). This might suggest that frontal thalamocortical circuits in these individuals are impaired in the capacity to effectively produce and synchronize γ -rhythms in response to external stimulation (Ferrarelli et al., 2008). Alternatively, it is possible that it is modulation (GABA_B mediated) rather than the generation of γ -oscillations that is dysfunctional in schizophrenia (Farzan et al., 2010). Modulation of γ -oscillations might be useful to shape the temporal profile of incoming information during different phases of cognitive tasks such as working memory (Farzan et al., 2010). Thus, selective deficits in the ability to modulate γ -oscillations may represent an important pathophysiological trait, which

may be responsible for some aspects of deficits commonly found in schizophrenia (Farzan et al., 2010).

4.2.2. Diagnosis

The TMS-EEG combination may also be useful for diagnostic purposes. Julkunen et al. (2008a) showed that cortical reactivity and connectivity were decreased in patients with Alzheimer's disease (AD). For patients with mild cognitive impairment (MCI), brain responses were frequently halfway between the values of controls and AD patients, consistent with the concept of MCI being a transitional state between normal aging and AD. Therefore, TMS-EEG might be sensitive to early functional changes in the diagnosis of MCI and AD.

Valentin et al. (2008) showed that, unlike in healthy subjects, TMS induces late responses (0.1s-1s) in patients with focal epilepsy which either resemble epileptiform discharges or the onset of a new rhythm clearly different from the background EEG. The induction of these late responses could be used to identify the epileptogenic region and diagnose the existence of a focal epilepsy (except if originating in deep insular or mesiotemporal cortex). It has therefore been suggested that the TMS-EEG methodology might be included in the routine diagnosis of focal epilepsy, complementary to interictal scalp EEG (Valentin et al., 2008).

4.2.3. Monitoring treatment outcome

The combination of TMS and EEG may also allow for the evaluation of the efficiency of antiepileptic rTMS treatment. Brodbeck et al. (2010) used EEG during rTMS treatment in patients with focal epilepsy to measure changes in spike-patterns and/or rate. The examined protocol (6Hz-primed rTMS at 1 Hz) failed to show consistent results in more than one patient. Rotenberg et al. (2010) suggest that the TMS-EEG combination might be used to fine-tune rTMS treatments in epilepsy, e.g. by adjusting the intensity to the TMS-EEG probed excitability of the stimulated area or by delivering TMS pulses at an appropriate timing relative to ongoing epileptiform activity. Concerning the latter "real-time" treatment approach, seizure identification triggering an anticonvulsive rTMS protocol have indeed proven to be realistic in rodents, which might pave the way for designing new tools for seizure detection triggering brain stimulation in humans (Rotenberg et al., 2010).

Real-time detection of an EEG-signature for triggering TMS pulses was also tested with the aim to improve rTMS treatment for depression. Price et al. (2010) designed an interactive rTMS method, whereby TMS pulses were applied in response to a selected pattern of background EEG analyzed in real time. Patients treated with this interactive method showed a trend toward greater recovery than the group treated with the standard 10 Hz rTMS method.

Although these studies remain exploratory and the to-be-targeted EEG-patterns leading to the best outcome are largely unknown, such results encourage the study of EEG-guided TMS for clinical application.

5. Improving TMS methodology

Finally, EEG measurements can provide the basis for more informed choices of TMS parameters, i.e. where, when, how much, and how long to stimulate. First, concerning the localization of stimulation, direct tracking of TMS outcome in brain space (e.g. via source estimates) could help to determine appropriate areas to stimulate when trying to disturb/enhance a brain area and/or task performance. Second, concerning the timing of stimulation, TMS could be triggered according to different time points of a previously recorded, task-related brain response (Thut et al., 2003). Third, EEG-guided TMS in real time could base the triggering of stimulation upon a predefined pattern recorded in the electroencephalogram (Price, 2004). Fourth, the intensity of stimulation, traditionally based on motor threshold (MT) or phosphene threshold (PT), could be adjusted on the basis of TEP-amplitude in “silent” brain areas. Fifth, the potentiation of brain response during rTMS (Brignani et al., 2008) might help to determine an appropriate duration of stimulation for reaching a clinical goal or avoiding critical stimulation safety levels. Interestingly, very low frequency rTMS (< 0.2 Hz), for which no cumulative effects on MEP amplitude have been described, has shown a potentiation of the N100 amplitude, suggesting some plasticity may still occur at this low frequency (Bender et al., 2005). Hence, the sensitivity of EEG could be used to track effects that otherwise might have been overlooked. This might be beneficial for improving TMS methodology in both neuroscientific and clinical research.

6. Concluding remarks

The use of EEG and TMS raises numerous technical challenges, many of which can be resolved with careful consideration. When thoughtfully designed, performed, and analyzed, TMS-EEG experiments can make a important contributions to the fields of cognitive and clinical neurosciences. Ultimately, TMS-EEG can contribute to questions regarding how TMS interacts with the brain to modify functions. TMS is a versatile neuroscientific tool and there is a virtually infinite space of TMS parameters that remain to be explored (Reithler et al., 2011). Combination of TMS with other neurophysiological techniques, e.g. EEG, fMRI and PET, can provide a better idea of how TMS interacts with brain activity, and more informed choices as to effective TMS parameters. This may, in turn, aid in the development

of better tools for diagnosis and rehabilitation. We believe that TMS-EEG will provide important new insights in the years to come.

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Figures

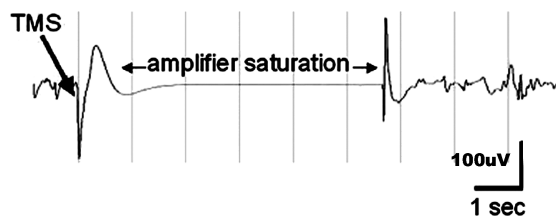


Fig. 1. Illustration of amplifier saturation after a single TMS pulse in a traditional EEG recording system. Adapted, with permission, from Ives et al. (2006).

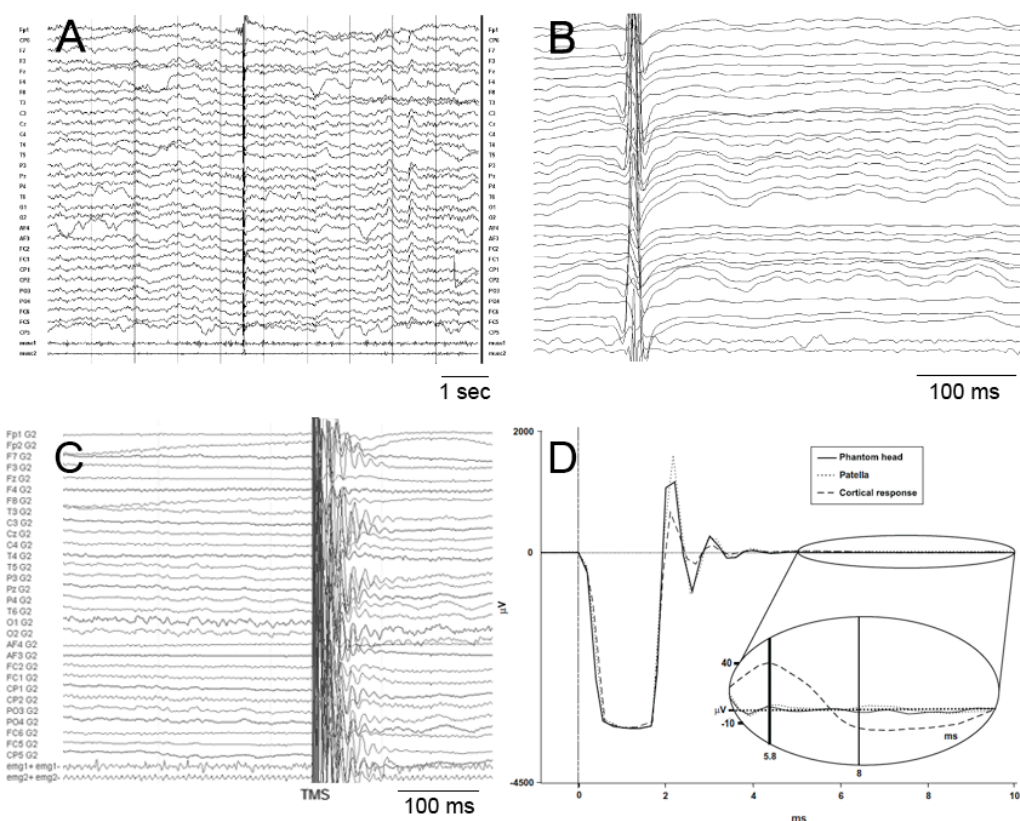


Fig. 2: Illustrations of immediate artifact recorded after TMS pulse. A and B. Saturation of amplifiers designed to work in MR environment after stimulation of M1 at 120% of MT. Adapted, with permission, from Fuggetta et al. (2005). C. Artifacts recorded with the same system. Adapted, with permission, from Morbidi et al. (2007). D. Artifacts recorded with a DC amplifier allowing to adjust the amplifier sensitivity and operational range to TMS. Stimulation of the phantom head was performed at 50% of MSO, stimulation of the patella at 40% and stimulation of the cortex at 57% (MT). Adapted, with permission, from Veniero et al. (2009).

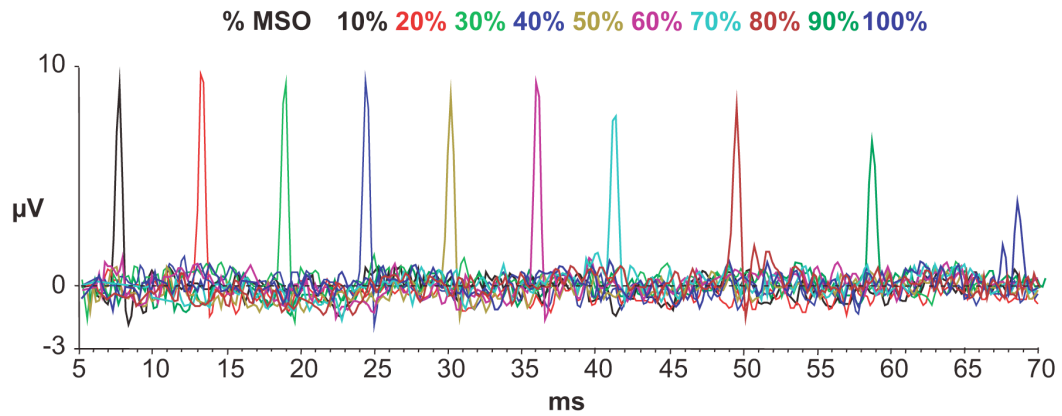


Fig. 3: Illustration of the amplitude and latency of the recharge artifact in function of stimulus intensity. Adapted, with permission, from Veniero et al. (2009).

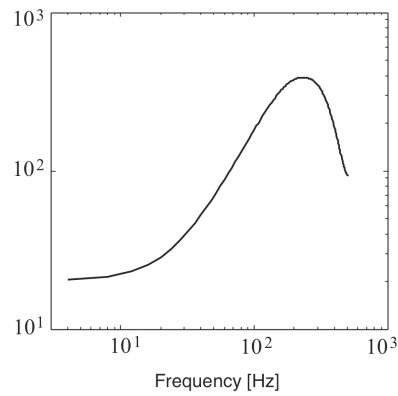


Fig. 4: Description of the artifact recorded on a manikin in the spectral domain. Adapted, with permission, from Morbidi et al. (2007).

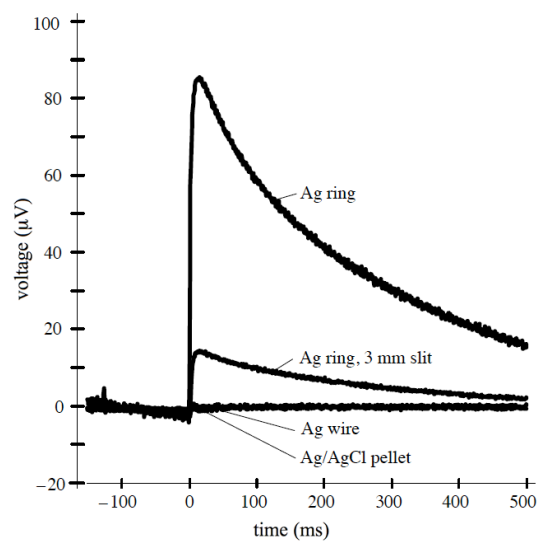


Fig. 5: Illustration of the slow decay of induced charges recorded with four types of electrode on a phantom. Adapted, with permission, from Virtanen et al. (1999).

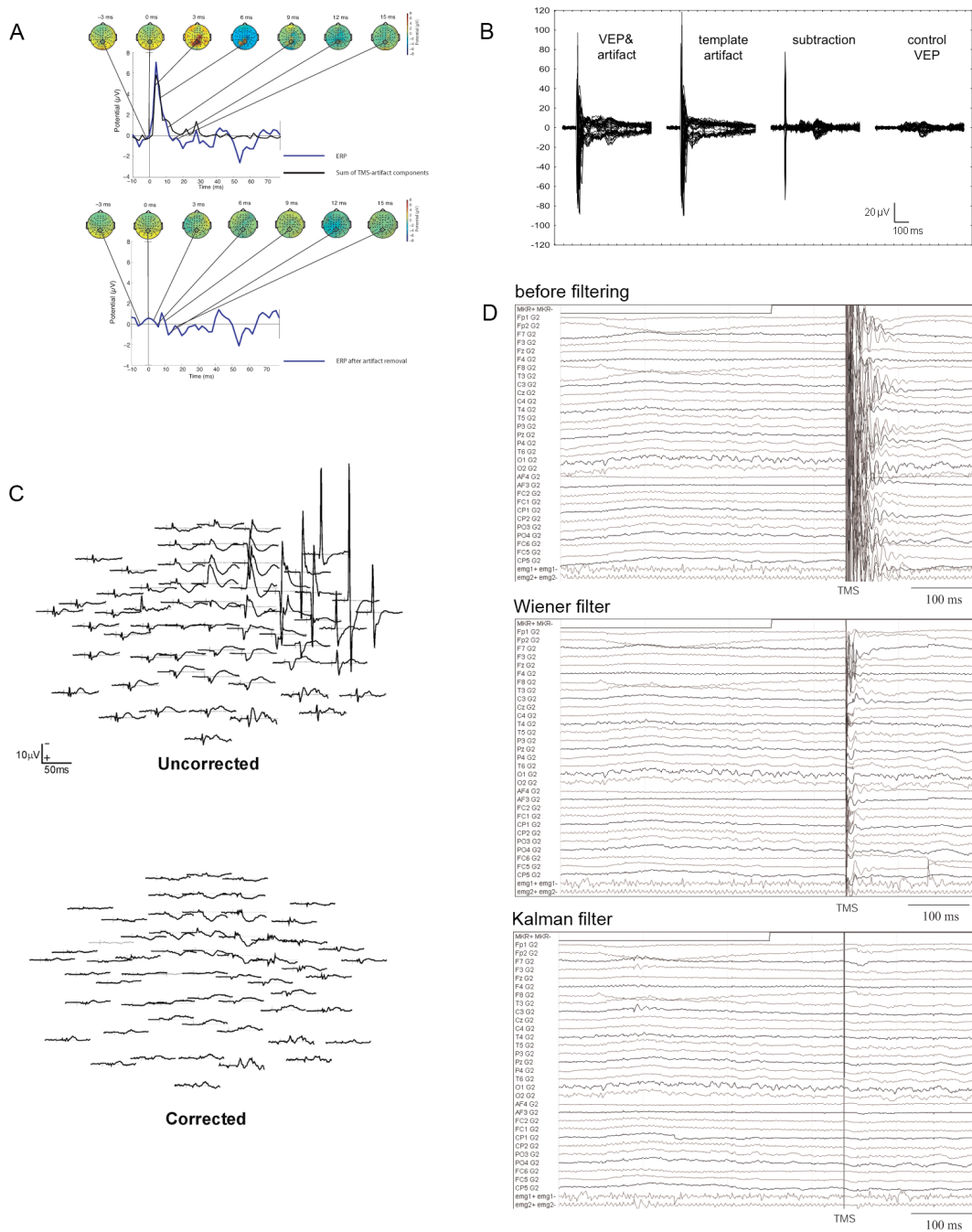


Fig. 6: Illustration of artifact removal efficiency. A. ICA method. Adapted, with permission, from Hamidi et al. (2010). B. Artifact-subtraction method. Adapted, with permission, from Thut et al. (2005). C. Brain topography and PCA method. Adapted, with permission, from Litvak et al. (2007). D. Filtering methods. Adapted, with permission, from Morbidi et al. (2007)

Tab. 1. Step-by-step guide to TMS-EEG

Points to consider	Methods proposed	Key references	Used by
Electrodes	Plastic pellet electrodes coated with a thin layer of silver epoxy (Ag/AgCl surface)	Virtanen et al. (1999)	
Amplifiers	Sample-and-hold	Ilmoniemi et al. (1997) Virtanen et al. (1999)	Paus et al. (2001) Komssi et al. (2004) Litvak et al. (2007) Hamidi et al. (2010)...
	Limited slew rate	Thut et al. (2003, 2005)	Ives et al. (2006)
	MR-EEG system	Fuggetta et al. (2005)	Morbidi et al. (2007)
	DC-amplifiers with wide dynamic range	Bonato et al. (2006)	Fuggetta et al. (2006) Fitzgerald et al. (2009) Levit-Binnun et al. (2010)
	DC-amplifiers with adjustable operational range	Brignani et al. (2008) Veniero et al. (2009)	
Synchronization between TMS discharge and EEG recordings	Synchronization box	Thut et al. (2003, 2005)	
Electrode and skin preparation	Low impedance	Veniero et al. (2009)	
	Mini puncturing technique	Julkunen et al. (2008b)	

Wire and coil placement	Procedure of wire rearrangement	Sekiguchi et al. (2010)	
Sound masking	Noise adjusted on the TMS click	Massimini et al. (2005)	Ferrarelli et al. (2008) Rosanova et al. (2009)
	Layer of foam between the coil and scalp to attenuate bone conduction	Massimini et al. (2005)	Ferrarelli et al. (2008) Rosanova et al. (2009)
Control conditions	Sham stimulation	Fuggetta et al. (2008)	
	Changing coil orientation	Bonato et al. (2006)	Thielscher et al. (2011)
	Real stimulation with no task	Thut et al. (2003; 2005)	
	Distracting tasks	Huber et al. (2008)	
Post-processing	Removing artifactual data (and reinterpolation)	Kahkonen et al. (2001) Fuggetta et al. (2005) Reichenbach et al. (2011)	
	Artifact subtraction	Thut et al. (2003; 2005)	Fuggetta et al. (2006) Reichenbach et al. (2011)
	PCA	Litvak et al. (2007)	Levit-Binnun et al. (2010)
	ICA	Hamidi et al. (2010)	
	Source reconstruction	Huber et al. (2008)	
	Fitting functions	Litvak et al. (2007)	

	Filtering	Morbidi et al. (2007)	
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