Transcranial Magnetic Stimulation and Electroencephalography

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Olivia Gosseries, Olivier Bodart, and Marcello Massimini

Contents

Abstract

Diagnostic assessment in severely brain-injured patients with disorders of consciousness is largely based on behavioral examinations. This approach can lead to misdiagnosis, giving rise to inaccurate prognosis and inappropriate treatment care. Concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) may provide a biological measure of the level of consciousness at the individual level by assessing functional integration and differentiation in the brain. Here we review a series of recent TMS-EEG studies that assess brain complexity in normal wakefulness, during physiological (sleep), pharmacological (anesthesia), and pathological (brain injury) conditions. TMS-EEG may contribute to unveiling the pathophysiology of disorders of consciousness due to severe acquired brain injury. This technique could also help clinicians in their decision making and provide support for treatment intervention.

10.1 Introduction

Behavioral examination is the current gold standard for the diagnosis of patients suffering from severe brain injury with disorders of consciousness (Bodart et al. 2013). However, this approach may be misleading as it relies on the

O. Gosseries (✉) • O. Bodart
Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liege, Sart-Tilman B30, Liege 4000, Belgium
e-mail: ogosseries@ulg.ac.be

Center for Sleep and Consciousness, and Postle laboratory, Departments of Psychiatry and Psychology, University of Wisconsin, Madison, WI, USA

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

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clinician to determine whether observed behaviors are reflex or volitional. The clinician may, for instance, not be aware of underlying motor, sensory, or cognitive impairments that can mask awareness. Behavioral and neuroimaging studies suggest that some patients considered to be unconscious at the bedside actually retain some conscious awareness (Monti et al. 2010; Schnakers et al. 2009). Establishing an accurate diagnosis of the level of consciousness is critical for ensuring accurate prognosis and for establishing the most appropriate plan of care. Yet, to date, there is no scientifically well-grounded measure of the level of consciousness that is independent of processing sensory inputs and producing appropriate motor outputs. Concurrent transcranial magnetic stimulation (TMS) and electroencephalography (EEG) may however provide a biological measure of the level of consciousness at the individual level, in pathological states but also in normal physiological and pharmacological conditions (Gosseries et al. 2014). In this chapter, we describe the basic principles of TMS-EEG technique and how this technique can aid in assessing cortical excitability, effective connectivity, and brain complexity in different conditions of (un)consciousness.

10.2 Transcranial Magnetic Stimulation

TMS is a noninvasive method of modulating the cortex using the principles of electromagnetic induction (Hallett 2000). Briefly, when a charge is passed through the wires of a TMS coil, a perpendicular magnetic field is produced. This field easily penetrates the skull and creates an electric current in the underlying cortex. TMS can be delivered through single, paired, or repetitive pulses that cause brief neuronal depolarization and discharge of action potentials (Lapitskaya et al. 2009b). Delivered over the motor or the visual cortex, single-pulse TMS induces motor evoked potentials (Lapitskaya et al. 2009a) or phosphenes (Kastner et al. 1998), respectively. Paired-pulse TMS and repetitive TMS can be used to assess cortical inhibition, facilitation, and plasticity. Repetitive TMS has been used to induce a sustained inhibition (<1 Hz) or activation (>1 Hz) of the neuronal population, which permits stimulation of brain areas and subsequent observation of behavioral and cognitive changes (Miniussi and Rossini 2011).

In the last several years, TMS has been combined with high-density EEG and a neuronavigation system (Fig. 10.1) to directly measure the activity of the brain itself, instead of measuring muscular activity or behavioral responses derived from the TMS stimulation. In this way, single-pulse TMS induces focal neuronal discharge at the cortex surface, and an EEG measures cortical electrical responses both locally and at distant sites (Fig. 10.2). This enables the study of cortical excitability (i.e., amplitude of the initial response to TMS) under the site of stimulation and long-range cortical effective connectivity (i.e., the overall effects of the perturbation) with good spatiotemporal resolution (Massimini et al. 2009). The neuronavigation system allows precise stimulation of a selected brain area and ensures stability of the position of the stimulation as well as reproducibility among different sessions (Casarotto et al. 2010). Studies demonstrated that reliable responses to cortical stimulation could be derived without being substantially affected by TMS-induced artifact thanks to new hardware solutions, improved EEG amplifier technology, and advanced data processing techniques (Rogasch and Fitzgerald 2013; Gosseries et al 2014). Using recent source modeling and statistical analyses, it is thus possible to detect the spatio-temporal dynamics triggered by a direct cortical stimulation in different conditions, such as normal wakefulness, sleep, anesthesia, and brain lesion (Casali et al. 2010, 2013).

10.3 Normal Wakefulness

During wakefulness, as shown in Fig. 10.2, TMS triggers sustained long-range and complex patterns of activation (Massimini et al. 2005). These TMS-EEG responses vary depending on

Fig. 10.1 Neuronavigated TMS-EEG system. The neuronavigation system is composed of a 3D head model and targeting system (*a1*), an infrared camera (*a2*), and glasses (*a3*) that are covered with reflective balls for infrared tracking. The stimulation coil (*b*) is also covered by these reflective balls for accurate localization of the stimulation point. The EEG system has a 60-electrode EEG net (*c*) connected to a compatible EEG amplifier and recording system (*d*). TMS-EEG: transcranial magnetic stimulation coupled with high-density electroencephalography (Taken from Napolitani et al. (2014))

the site of stimulation, because each brain area tends to preserve its own natural frequency (Rosanova et al. 2009). For instance, TMS consistently evoked alpha-band oscillations (8–12 Hz) in the occipital cortex, beta-band oscillations (13–20 Hz) in the parietal cortex, and fast beta/gamma-band oscillations (21–50 Hz) in the frontal cortex (Rosanova et al. 2009). Brain regions tend to oscillate at their natural frequencies also when indirectly stimulated by TMS, via cortical connections. More recently, cortical excitability has been shown to increase with time awake (Huber et al. 2013). Short-term memory tasks have also been found to increase the strength and the spatial spread of the electrical currents induced by TMS (Johnson et al. 2012). Finally, training on a working memory task increases effective connectivity across frontoparietal and parietooccipital networks (Kundu et al. 2013).

10.4 Sleep

Navigated TMS-EEG has also been used to study the transition from wakefulness to sleep. When TMS is applied during non-REM (NREM) sleep, a state where awareness is typically massively reduced, it triggers a large positive-negative wave that usually stays localized under the stimulation coil and dissipates quickly (Massimini et al. 2005). In this condition, increasing the stimulation intensity results in a global positive-negative wave much like spontaneous NREM sleep slow waves (Massimini et al. 2007). This stereotypical response still

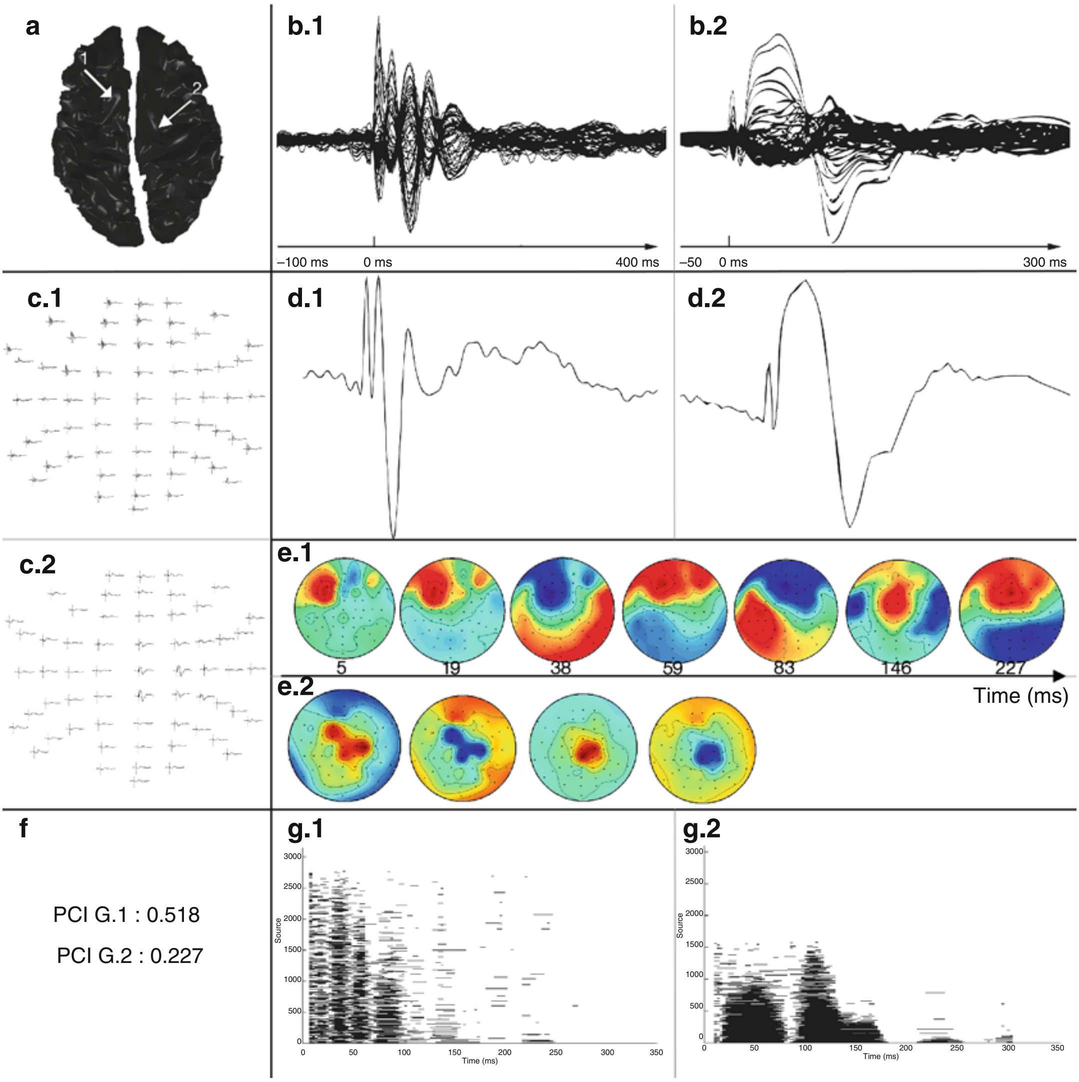

Fig. 10.2 Typical TMS-EEG findings in conscious and unconscious states. (**a**) Stimulation target (*arrow*) on the subject's brain (1 = healthy subject, 2 = patient in a vegetative state/unresponsive wakefulness syndrome). (**b**) Average TMS-EEG response over the 60 electrodes in a healthy awake subject (**b1**) and in a patient in a vegetative state/unresponsive wakefulness syndrome (**b2**). (**c**) TMS-EEG response across space (i.e., channels) for the healthy subject (**c1**) and the unconscious patient (**c2**). (**d**) Typical TMS-EEG response under the stimulation coil in conscious (**d1**) and unconscious states (**d2**). (**e**) Change in the localization of maximum activity across time on EEG topography plots (**e1** for conscious and **e2** for unconscious state). (**g**) Binary matrices of significant source activation across time for both consciousness (**g1**) and unconsciousness (**g2**). The compression of these matrices helps computing the perturbational complexity index (PCI) (**f**)

lacks the complexity of the response observed in wakefulness, suggesting that while the thalamocortical system remains reactive during NREM, it loses its capacity to generate differentiated patterns of neural activity. In REM sleep, even though the brain is isolated from the external world, awareness can be present under the form of vivid dreams that can be reported verbally immediately after awakening. The TMS-EEG response in REM is a complex and widely distributed, high-frequency response that is quite similar to the one observed during wakefulness

(Massimini et al. 2010). This suggest that the complexity of cortico-cortical casual interactions may signal consciousness independently of sensory access and motor outputs.

10.5 General Anesthesia

In addition to physiological shifts, transition from wakefulness to unconsciousness can be driven by means of pharmacological agents. When performed on subjects under midazolam-induced general anesthesia, TMS triggers a large positive-negative wave that stays localized under the stimulation coil and vanishes rapidly (Ferrarelli et al. 2010). This response is very similar to the one observed in the NREM sleep. Likewise, when subjects are awakened from midazolam general anesthesia, they cannot report any conscious content (Bulach et al. 2005). Midazolam acts exclusively on GABA-A receptor and thus is likely to inhibit the thalamocortical system, preventing it to engage in a widespread differentiated communication with distant cortical areas, which leads to unconsciousness. When subjects awake from this unconscious state, with tapering doses of midazolam, TMS-EEG responses become more and more complex and widespread, recovering the characteristics observed in healthy awake subjects.

10.6 Severe Brain Injury

Another population subject to unconsciousness is represented by patients with severe brain injuries. Different disorders of consciousness compose this population, and solely based on clinical evaluation, it can be challenging to disentangle patients with an unresponsive wakefulness syndrome (formerly known as vegetative state) from those who are in a minimally conscious state (Schnakers et al. 2008). While both are awake and show some sort of sleep–wake cycle, the former only show reflexive responses to stimulations (Laureys et al. 2010), while the latter show minimal signs of consciousness such as visual pursuit or response to command (Giacino et al. 2002). Neither can, by definition, communicate nor report their (un)consciousness. Performed on patients with a vegetative state/unresponsive wakefulness syndrome, who show no signs of consciousness, TMS triggers the stereotypical local, slow, and short-lasting wave that has been observed in NREM sleep and general anesthesia (Fig. 10.2). Sometimes, no responses at all can be elicited, especially in patients with post-anoxic brain injuries. On the other hand, patients in a minimally conscious state, who show limited but reproducible signs of consciousness, invariably respond to TMS with a more complex, widespread, high-frequency wave very similar to the one observed in wakefulness (Rosanova et al. 2012). In patients with a locked-in syndrome, who are fully conscious but completely paralyzed except for eye movement, TMS triggers the same complex response we have previously observed in healthy awake subjects (Rosanova et al. 2012). These results indicate a clear-cut difference of TMS response between unresponsive and minimally conscious patients, which has also been confirmed recently (Ragazzoni et al. 2013).

A subset of severe acquired brain-injured patients was also evaluated several times in the acute setting. The first assessment took place 48 h after the end of sedation, as they emerged from coma, whereas the second TMS recording was performed either when they improved from vegetative state/unresponsive wakefulness syndrome to minimally conscious state (three patients) or after at least 30 days if there was no recovery of consciousness (two patients). The last recording was set up as soon as the three patients who improved recovered functional communication (i.e., emergence of the minimally conscious state). In the first TMS assessment, all patients were awake but unconscious and four of them demonstrated a stereotypical slow and local positive-negative wave, similar to the response observed in chronic unresponsive patients. The fifth patient did not demonstrate any TMS-EEG response. When the patients recovered signs of consciousness and communication, the TMS-EEG response regained characteristics seen in healthy awake subjects, being more complex and widespread than previously observed in the same subject. Interestingly, one of the patients who improved to minimally conscious

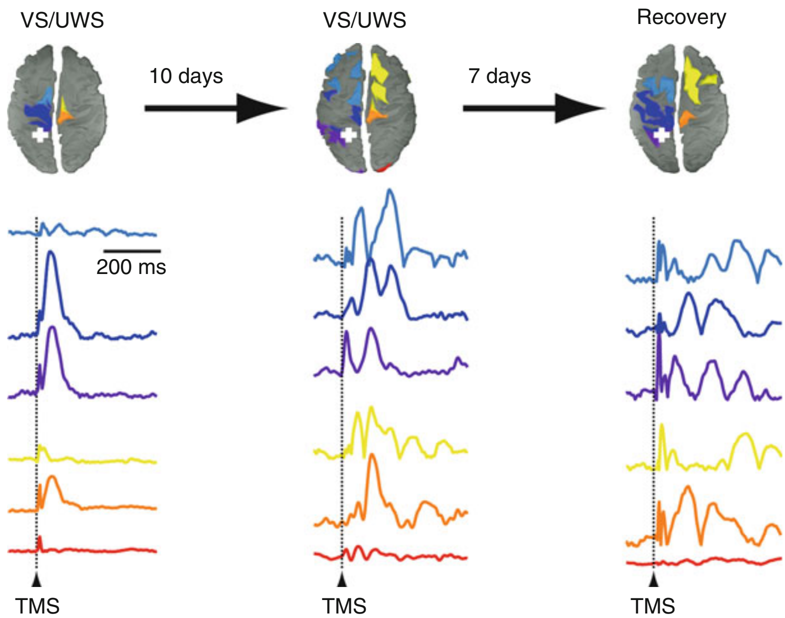

Fig. 10.3 Recovery of coma and TMS-EEG responses. Recovery of consciousness in a patient with severe brain injuries is accompanied by the recovery of complex, widespread, and differentiated EEG activations in response to TMS, depicted here at the cortical source level (*colored traces*) (Taken from Sarasso et al. (2014)). *VS/UWS* vegetative state/unresponsive wakefulness syndrome

state was behaviorally back in an unresponsive state on the day of the examination, but widespread and complex brain responses could still be detected, even if at the bedside, no sign of consciousness could be observed (Fig. 10.3). The two patients who did not recover signs of consciousness and remained in an unresponsive state did not show any modification of their TMS-EEG responses. Although based upon a limited number of patients, these observations are important as they show that TMS-EEG is sensitive to changes in the consciousness level, and that it has the advantage to be applied at the bedside of patients with acquired severe brain injuries.

10.7 Measuring the Level of Consciousness

Clinical application of this technique could be made even more accessible with the recent development of newer analysis techniques. Indeed, so far the distinction between conscious and unconscious subjects was mainly based upon a careful inspection of the TMS response. More objective quantitative approaches can be designed to allow researchers to easily compare different subjects and conditions. General indices reflecting cortical excitability and effective connectivity were first developed (Casali et al. 2010). However, these indices do not allow a direct comparison between subjects. For this reason, the perturbational complexity index (PCI) was recently developed (Fig. 10.2). PCI is computed starting from TMS-evoked potentials by (1) extracting the source model of cortical activation from the preprocessed scalp EEG signal, then (2) running a permutation statistical test to detect significantly activated source and plotting them against time in a binary matrix (3) compressing this matrix using a Lempel–Ziv algorithm and normalizing the data. This approach has been tested on more than a hundred TMS-EEG sessions on healthy subjects in various conscious and unconscious states, as well as in patients with chronic disorders of consciousness. It appears that PCI can distinguish, at the single-subject level, between conscious (healthy awake subjects, locked-in patients and minimally conscious patients), and unconscious conditions (vegetative state/unresponsive wakefulness patients, healthy subjects under general anesthesia using midazolam, xenon, and propofol and during NREM sleep) (Casali et al. 2013). This may open the doors to an easy-to-use system to objectively assess brain's capacity for consciousness, hopefully helping clinicians make accurate treatment decisions and discuss the patient's state with their relatives.

10.8 Conclusion

Differentiating between conscious and unconscious patients still represents a major clinical, ethical, and medicolegal challenge. While behavioral assessment remains the current clinical standard for detecting awareness, it cannot stand alone any longer as recent studies have reported that patients considered unconscious at the bedside can have preserved awareness (Cruse et al. 2011; Stender et al. 2014). The TMS-EEG technique may provide a neurophysiological measure of the level of consciousness at the single-subject level in physiological, pharmacological, and pathological conditions. The basic evidence is that, during conscious states, such as normal wakefulness, REM sleep, minimally conscious state, and locked-in syndrome, the brain is able to sustain long-range and complex activity patterns marked by a differentiated, diffuse, and long-lasting evoked response, which gives a high value of PCI. During unconscious states, such as NREM sleep, anesthesia, and vegetative state/unresponsive wakefulness syndrome, TMS triggers a stereotypical, local, and short-lasting response, which gives a low value of PCI (Fig. 10.2). Importantly, this technique can be used at the bedside and does not require the participation of the subject, neither requires language processing nor functioning afferent/efferent pathways, which is of particular interest when assessing patients with severe brain injuries. Further studies should confirm these inaugural results on a larger sample. Only then, this technique may be incorporated into the clinical routine in order to help the diagnosis, prognosis, and treatment monitoring of patients with disorders of consciousness.

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