Sleep Medicine xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Transcranial magnetic stimulation and sleep disorders: pathophysiologic insights

Raffaele Nardone [a,b,*], Yvonne Höller [a], Francesco Brigo [b,c], Frediano Tezzon [b], Stefan Golaszewski [a], Eugen Trinka [a]

[a] Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria
[b] Department of Neurology, Franz Tappeiner Hospital, Merano, Italy
[c] Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Italy

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Transcranial magnetic stimulation
Insomnia
Obstructive sleep apnea
Restless legs syndrome
Periodic limb movements
Narcolepsy
Posttraumatic sleep–wake-disorders
REM sleep behavior disorder

ABSTRACT

The neural mechanisms underlying the development of the most common intrinsic sleep disorders are not completely known. Therefore, there is a great need for noninvasive tools which can be used to better understand the pathophysiology of these diseases. Transcranial magnetic stimulation (TMS) offers a method to noninvasively investigate the functional integrity of the motor cortex and its corticospinal projections in neurologic and psychiatric diseases.

To date, TMS studies have revealed cortical and corticospinal dysfunction in several sleep disorders, with cortical hyperexcitability being a characteristic feature in some disorders (i.e., the restless legs syndrome) and cortical hypoexcitability being a well-established finding in others (i.e., obstructive sleep apnea syndrome narcolepsy). Several research groups also have applied TMS to evaluate the effects of pharmacologic agents, such as dopaminergic agent or wake-promoting substances.

Our review will focus on the mechanisms underlying the generation of abnormal TMS measures in the different types of sleep disorders, the contribution of TMS in enhancing the understanding of their pathophysiology, and the potential diagnostic utility of TMS techniques. We also briefly discussed the possible future implications for improving therapeutic approaches.

1. Introduction

Transcranial magnetic stimulation (TMS) can be applied with different paradigms to obtain direct measures of cortical excitability [1–4]. These TMS paradigms can be used to obtain indirect but valuable information regarding the function of various neurotransmitter systems and may provide insights into the complex pathophysiology of sleep disorders.

In our paper, we review the most relevant studies reporting the applications of TMS techniques to characterize important neurophysiologic and pathophysiologic aspects of the most common sleep disorders. Herein, we update a previous review of Civardi et al. [5], as many other studies have extended the previous findings in the last few years, and TMS techniques have been applied in other important sleep diseases, including sleepwalking, rapid eye movement (REM) sleep behavior disorder (RBD), posttraumatic sleep–wake disturbances (SWD), and chronic idiopathic insomnia. Thus we aimed to provide a comprehensive perspective of past and current research and to help guide future studies (Table 1).

The MEDLINE, accessed by PubMed (1966–April 2012) and EMBASE (1980–April 2012), electronic databases were searched using the medical subject headings *Sleep medicine*, *Sleep disorders*, and *Transcranial magnetic stimulation*, as well as following free terms combined in multiple search strategies with Boolean operators to find relevant articles: *motor threshold*, *central motor conduction*, *motor cortex excitability*, *cortical silent period*, *intracortical inhibition*, *intracortical facilitation*, *afferent inhibition*, *insomnia*, *functional connectivity*, *cortical plasticity*, *obstructive sleep apnoea* (or *apnea*) *syndrome*, *restless legs syndrome*, *periodic limb movements*, *narcolepsy*, *sleepwalking*, *posttraumatic sleep–wake-disorders*, *REM sleep behavior disorder*, and *chronic insomnia*.

2. Methods: measures of cortical excitability, connectivity, and plasticity

2.1. Motor threshold

Resting motor threshold (RMT) is defined as the minimum stimulus intensity which is required to produce a motor-evoked

* Corresponding author. Address: Department of Neurology, "F. Tappeiner" Hospital – Meran/o, Via Rossini, 5, 39012 Meran/o (BZ), Italy. Tel.: +39 0473 264616; fax: +39 0473 264449.
E-mail address: raffaele.nardone@asbmeran-o.it (R. Nardone).

1389-9457/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.sleep.2013.04.025

potential (MEP) of more than 50 μV in at least five of 10 consecutive trials at rest, whereas active-motor threshold (AMT) is the minimum stimulus intensity that produces a MEP (approximately 200 μV in at least 5 of 10 consecutive trials) during isometric contraction of the tested muscle at approximately 10% of maximum voluntary contraction. RMT is thought to provide information about a central core of neurons in the muscle representation of the primary motor cortex. RMT is increased by drugs that block voltage-gated sodium channels [6], is not affected by drugs with effects on gamma-aminobutyric acid (GABA) [7], and is lowered by drugs increasing non-*N*-methyl-D-aspartate (NMDA) glutamatergic transmission [8]. These findings suggest that RMT reflects both neuronal membrane excitability and non-NMDA receptors glutamatergic neurotransmission. Motor threshold typically is increased if a significant portion of the corticospinal tract is damaged, while it decreases in situations of a hyperexcitable corticospinal system.

2.2. Central motor conduction time

Central motor conduction time (CMCT) is defined as the latency difference between the MEPs induced by motor cortex stimulation and those evoked by spinal (motor root) stimulation. CMCT (measured in milliseconds) is calculated by subtracting the peripheral conduction time from spinal cord to muscles from the absolute latency of responses evoked by cortical stimulation with the following formula: MEP latency − (F latency + M latency − 1)/2 [9]. Lengthening of CMCT suggests demyelination of the fastest conducting corticomotoneuronal fibers, while low amplitude responses with little delay or absence of responses are more suggestive of neuronal or axonal loss [1]. However, another frequent cause of CMCT lengthening is axonal destruction or degeneration of fastest conducting corticomotoneuronal fibers, such as in stroke, motor neuron disease, or compressive myelopathy.

2.3. MEP amplitude

Similar to the motor threshold, the MEP amplitude reflects the density of corticomotoneuronal projections onto motor neurons, but it possibly assesses the function of the neurons that are less excitable or further away from the center of the TMS-induced electrical field [10]. MEP amplitude is thought to reflect the summation of complex corticospinal volleys consisting of D (direct) and I (indirect) waves [11,12].

2.4. Contralateral silent period

If TMS is delivered while the subject voluntarily contracts the target muscle, the MEP is followed by a silence of the voluntary electromyography (EMG) activity, which is called contralateral cortical silent period (CSP). Spinal inhibition contributes to the early phase of the CSP (its first 50–75 ms), whereas the late one reflects a suppression of corticospinal output at a cortical level.

The duration of the CSP is compatible with a long-lasting inhibition mediated by $GABA_B$ [13,14].

2.5. Intracortical inhibition and facilitation using paired TMS

TMS also may be used to investigate the intracortical inhibitory and facilitatory mechanisms in the motor cortex. Some of these TMS techniques involve paired stimuli based on a conditioning test paradigm [15]. Stimulation parameters such as the intensity of the conditioning (CS) and test stimulus (TS), together with the time between them (interstimulus interval [ISI]), determine interactions between stimuli. When the CS is below and the TS is above the motor threshold, the CS inhibits the response to TS at ISIs of 1–5 ms (short-latency intracortical inhibition [SICI]) while inducing an increase in the test MEP amplitude at ISIs of 7–20 ms (intracortical facilitation [ICF]). SICI is thought to mostly reflect the excitability of inhibitory GABAergic cortical circuits [1,16] and is associated with a reduction in the number and amplitude of late I waves with I-wave suppression remaining up to an ISI of 20 ms, which corresponds to the duration of the inhibitory postsynaptic potentials mediated through $GABA_A$ receptors [17,18]. Conversely, ICF is considered to depend on the activity of intracortical glutamatergic excitatory circuits [19,20]. In fact, glutamate is the main excitatory neurotransmitter in the human central nervous system and mediates synaptic transmission primarily by activation of the α-amino-3-hydroxy-5-methylisoxazole-4-propionate/kainate receptors and the NMDA receptors.

In a separate paired-pulse paradigm, consisting of suprathreshold stimuli, CS and TS are measured by the long-latency intracortical inhibition (LICI) [21]. In healthy subjects, LICI typically occurs at ISIs between 50 and 200 ms when stimulus is adjusted to produce an MEP amplitude of approximately 1 mV. Therefore, LICI is a long-lasting inhibition, which is similar to the CSP. Accordingly, it has been demonstrated that LICI is mediated by slow inhibitory postsynaptic potentials via activation of the $GABA_B$ receptor [14].

2.6. Short-latency afferent inhibition

Short-latency afferent inhibition (SAI) refers to the suppression of the amplitude of a MEP produced by a conditioning afferent electrical stimulus applied to the median nerve at the wrist approximately 20 ms prior to TMS of the hand area of the contralateral motor cortex [22]. SAI is thought to reflect the integrity of central cholinergic neural circuits, as it has been shown to be reduced or abolished by the muscarinic antagonist scopolamine in healthy subjects [23] and is positively modulated by acetylcholine [24]. On the other hand, it has been suggested that SAI may depend on the integrity of circuits linking sensory input and motor output [25], and other neurotransmitters, in particular dopamine, are supposed to play a modulatory role on the cholinergic transmission.

2.7. Cortical connectivity and plasticity measures

Integration of TMS with electroencephalography (EEG) [26–28] has the potential to provide realtime information on cortical reactivity and distributed network dynamics through the analysis of TMS-evoked potentials. Cortical responses to repetitive TMS and paired-associative stimulation (PAS) provide information on different aspects of cortical plasticity [1,29,30].

PAS in humans involves a stimulus to a peripheral nerve (usually the median nerve) followed by a single TMS pulse applied over the hand area of the motor cortex [31]. PAS induces a lasting increase in corticospinal excitability, which can be considered a marker of motor cortical plasticity, with long-term plasticity-like mechanisms thought to play a major role [31].

In addition, TMS can even influence brain function if it is repetitively delivered. Repetitive TMS (rTMS) consists of the application of a train of TMS pulses of the same intensity to a single brain area at a given frequency that can range from 1 to 20 or more stimuli per second and is capable of modulating cortical excitability and inducing long-lasting neuroplastic changes.

Depending on the stimulation parameters, particularly the frequency of stimulation, cortical excitability can be modulated and rendered facilitated or suppressed. Generally low-frequency rTMS (stimulus rates of $\leqslant$1 Hz) induces inhibitory effects on motor cortical excitability allowing creation of a reversible virtual lesion [32], while high-frequency rTMS (5–20 Hz) usually promotes an increase in cortical excitability [33,34]. This modulation can last for several minutes depending on the duration of the train itself and also provides an index of plasticity.

Please cite this article in press as: Nardone R et al. Transcranial magnetic stimulation and sleep disorders: pathophysiologic insights. Sleep Med (2013), http://dx.doi.org/10.1016/j.sleep.2013.04.025