CLINICAL REVIEW

Applications of transcranial magnetic stimulation in sleep medicine

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KEYWORDS
Transcranial magnetic stimulation; Motor cortex; Sleep; Pathophysiology; Diagnosis; Treatment

Summary
Transcranial magnetic stimulation (TMS) is a new method, developed nearly 20 years ago, that allows the study of cortical excitability. The whole brain undergoes profound changes in sleep. Motor evoked potentials (MEPs) have been used to trace the effects of sleep on cortical excitability and to the corticomotoneur connections. Although in the past some technical aspects limited the application of TMS in sleep, recently we observed a new explosion of interest in this field. The main body of data was gathered on sleep physiology, but its diseases or syndromes were also studied in detail. Many single and paired pulse-TMS variables were applied. Moreover, TMS variables were investigated as a potential tool for the diagnosis or the differential diagnosis of sleep disorders. In the recent years, the advent of repetitive TMS offered some therapeutic perspectives, which are under current investigation in few of these disorders. Combining repetitive TMS with electroencephalogram (EEG) represents a new and probably useful approach to sleep. Among the main entities classified in the sleep disease group, the following were subject to TMS studies: obstructive sleep apnoea syndrome (OSAS), propriospinal myoclonus, restless legs syndrome (RLS) with periodic limb movement and narcolepsy. For each of these, we examine the applications of TMS separately.

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Abbreviations: aT, active threshold; CMCT, central motor conduction time; CSP, central silent period; DLPFC, dorsolateral prefrontal cortex; GABA, gamma-amino-butyric-acid; ICE, intracortical excitability; ICF, intra–cortical facilitation; ISI, interstimulus interval; MEPs, motor evoked potentials; OSAS, obstructive sleep apnoea syndrome; p-TMS, paired pulse TMS; RLS, restless legs syndrome; rT, relaxed threshold; rTMS, repetitive transcranial magnetic stimulation; SD, sleep deprivation; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; SWA, slow wave activity; s-TMS, single pulse-TMS; TMS, transcranial magnetic stimulation.

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Introduction

Transcranial magnetic stimulation (TMS) is a widely used non-invasive neurophysiological technique able to assess painlessly and safely motor cortex excitability. Since the last 20 years, many researchers investigated the responses to electromagnetic stimulation of the primary motor cortex in a number of different physiological and pathological states. TMS has proved its validity in clinical practice as diagnostic tool in many neurological diseases such as: multiple sclerosis, myelopathies, amyotrophic lateral sclerosis, Parkinson’s disease, stroke and psychogenic paralysis. TMS was also useful in epilepsy and in the evaluation of drug mechanism of action, although these applications were limited to the research field. Although application of TMS in sleep study has been very scarce, in the recent years we observed a new increasing interest in this field. The main body of data was gathered on sleep physiology, but its diseases or syndromes were also studied in detail. During sleep the brain and thus the motor system undergo profound changes. These are different for sleep stages and depend on rhythmic oscillation of cortical, thalamic and brainstem structures as shown by animal and human research. Muscular activity changes through the different sleep stages as well. On this basis, motor evoked potentials (MEPs) were then used to trace the effects of sleep onto the corticomotoneuron connections. Various TMS variables were investigated as a potential tool for the diagnosis or the differential diagnosis of sleep disorders. Finally, the advent of repetitive transcranial magnetic stimulation (rTMS) offered some therapeutic perspectives, which are under current investigation in few of these disorders.

TMS

Single pulse-TMS (s-TMS)

s-TMS was originally developed by Barker et al. Serial capacitors discharge through a wire coil a high peak (5000 A) and a very brief (100 μs) electrical pulse. The rapid changes of the magnetic field induce a weak electrical current in conductive structures of the cerebral cortex. Activation of corticospinal neurons occurs, leading to a muscle twitch, that has an electrical counterpart. This, when recorded by surface electrodes, is termed the motor evoked potential (MEP). Spread of the stimulus to different muscles depends on stimulus intensity, site of application and characteristics of the coil (size and shape). Large round coils are less focal than ‘figure-of-eight’ or ‘butterfly’ coils. In monophasic stimulators, the current direction in the coil becomes crucial for the preferential activation of one hemisphere. For instance, the anti-clockwise current flowing in a round coil is elective for the left hemisphere. A ‘figure-of-eight’ coil, with the handle pointed backwards at an angle of 45° from the midline, can induce a postero-anterior current, that is more effective for activation of the motor strip. When the coil is placed over the vertebral column, it stimulates motor roots at their exit from the intervertebral foramina, evoking muscles twitches. Several variables can be measured using TMS, such as threshold, amplitude, duration, cortical and peripheral latency, central motor conduction time (CMCT) and central silent period (CSP). TMS activates corticospinal neurons mainly trans-synaptically, through excitatory interneurons. As shown below, this largely indirect action of s-TMS on the projection neurons is the basis for its use as a probe of human motor cortex excitability, both in physiology and pathophysiology. The following main MEP variables have been studied in sleep medicine: threshold to stimulation, cortical latency, CMCT, MEP amplitude and CSP.

Threshold to stimulation

This variable expresses the minimum intensity capable of evoking MEPS in a given target muscle, which is usually at rest (relaxed threshold—rT), or voluntarily preactivated (active threshold—aT). Threshold is expressed as a percentage of the stimulator maximum output power. According to the guidelines of the International Federation of Clinical Neurophysiology, the rT is “the minimum stimulus intensity able to elicit an MEP 50–100 μV in amplitude occurring in 50% of 10–20 consecutive responses, with a signal gain of 50 μV/cm”. The aT has a similar definition, but the minimal response size may be around 200–300 μV because of the difficulty in distinguishing it from the background activity. Although threshold is intrinsically affected by many stimulator characteristics (maximum output power, mono versus polyphasic waveform, and rise time of the magnetic pulse, coil shape and position, etc.), it has been widely used as an index of the cortico-motoneuron system excitability. Pharmacological studies suggest that it reflects, at least in part, the permeability of membrane Na/K+ voltage-gated ion channels of motor cortical neurons. Relaxed threshold largely reflects the excitability of presynaptic cortical axons. The physiological meaning of aT is even more complex, since during voluntary contraction,
the entire cortico-motoneuron connection enhances its excitability and postsynaptic phenomena likely play a more important role. Anyway, because of the (at least) disynaptic nature of the descending pathway tested, threshold is also a function of the alpha-motoneuron excitability.

Cortical latency and central motor conduction time

The (minimum) cortical latency of the MEP is the time between a high-intensity magnetic stimulus and the MEP rise in the preactivated target muscle. CMCT represents the time taken by the fastest volley of corticospinal neurons to reach the alpha-motoneurons. Thus, it is an indirect index of the maximum conduction velocity of corticospinal axons. It can be calculated by subtracting from the (minimum) cortical MEP latency the (minimum) peripheral latency (CMCT = cortical latency – spinal latency), in alternative, the latency of the F-wave can be used.

MEP amplitude

Peak-to-peak MEP size increases proportionately to the stimulus intensity according to the laws of pyramidal tract conduction reaching its maximum when the target muscle is active at 10% or more of the maximum voluntary contraction. When stimulus intensity and muscle pre-activation are constant, the MEP size reflects synchronization and number of alpha-motoneurons that finally discharge in response to the cortical shock. Thus, it has been used as another index of the overall excitability of the cortico-motoneuron connection.

Central silent period

The CSP represents an electromyographic silence of variable length (up to 100–300 ms) that follows the MEP when the target muscle is pre-activated. This ‘negative’ phenomenon has a complex and partly obscure neurophysiologic origin. Normally, there is a direct relationship between its duration and the stimulus intensity. Many segmental and suprasegmental inhibitory effects contribute to the EMG silence. Segmental phenomena would play a role in the early portion of CSP, instead in the later portions they are more clearly supraspinal, depending on a lack of excitatory drive onto the spinal alpha-motoneurons. This has been attributed to inhibitory phenomena induced in motor cortical areas mediated by GABA-β receptors. In any case, the silent period has been used as a further index of cortico-motoneuron excitability in a wide range of normal and disease states.

Paired pulse TMS (p-TMS)

The methodology of p-TMS dates back to the early 1990s. It is capable of studying a number of physiological phenomena, such as ipsilateral intracortical excitability, transcallosal inhibition and cerebellar inhibition. With respect to sleep, most studies have dealt with ipsilateral intracortical excitability at short interstimulus intervals (ISI). Two different stimuli are delivered to the motor cortex through the same coil, separated by a variable ISI. The first (conditioning) stimulus is submotor threshold—usually 80% of the relaxed threshold—the second (test) stimulus is such as to evoke an MEP of about 1 mV in amplitude; different phenomena occur depending on the ISI. For ISIs of 1–6 ms, the ‘test’ MEP is smaller, while it is greater for ISIs of 8–16 ms (or slightly longer). A typical biphasic curve can then be plotted, where the former phase depicts the inhibition or intracortical inhibition period (SICI) of the test MEP and the latter depicts its facilitation or intracortical facilitation period (SICF). A series of demonstrations concluded that these phenomena originate from activation of interneurons intrinsic to the primary motor cortex. The term intracortical (cortico-cortical) inhibition and facilitation arose, altogether indicated as ‘intracortical excitability’. The physiologic background of these opposite effects is due to different interneuron populations, through GABAergic modulation. Drugs that enhance the brain GABAergic tone depress intracortical facilitation and enhance intracortical inhibition. According to the most recent researches, the short-interval intracortical inhibition would be under the influence of the GABAa receptor population. Another method of p-TMS concerns the inhibition of contralateral motor cortex via corpus callosum. Two suprathreshold magnetic focal stimuli, one delivered over each hemisphere, are used. When the conditioning stimulus precedes the test stimulus by 5–30 ms, the response to the test stimulus is reduced. Inhibition depends on stimulus intensity and age. Moreover it shows a gradient dominant > non-dominant hemisphere. Long-interval intracortical inhibition can be tested with paired-pulse technique delivering two suprathreshold pulses, with the same intensity, at a longer ISI (50–300 ms). Inhibition of the test MEP is observed at ISIs of 100–200 ms, and shares with CSP the same GABAa-mediated cortical mechanisms.

Repetitive TMS (r-TMS)

Magnetic pulses can be delivered to brain structures in a repetitive way through specific devices.
Repetition rate is very important for the physiologic effects. Conventionally, slow r-TMS is below a frequency of 1 Hz, while rapid-rate r-TMS is above 1 Hz. Other important variables are the number of pulses, duration of the trains, repetitions and stimulus intensity. Repetitive TMS, especially in its rapid-rate variety, raises some safety concerns, because of its documented capability to induce epileptic phenomena, even in normal subjects. On this basis, the international scientific community published ad-hoc safety guidelines for the use of r-TMS. The spectrum of the physiological and clinical applications of r-TMS is particularly complex, in proportion to the complexity and variety of the stimulus protocols adopted, including the site of stimulation. For instance, slow r-TMS was shown to have a depressing effect on motor cortical structures that outlasted the stimulation itself. For this reason, the method is currently under investigation for a potential beneficial effect in the treatment of epilepsy syndromes, Parkinson’s disease and dystonia. Then there is evidence supporting the usefulness of rapid-rate r-TMS in the treatment of depression.

Sleep (Table 1)

TMS was applied mainly in sleep physiology. The first paper was published in the late eighties by Hess et al. They compared cortical excitability changes in REM and NREM sleep. This first study gave rise to several other studies.

Single-pulse transcranial magnetic stimulation

The following main MEP variables were studied in sleep: threshold to stimulation, corticomotor conduction time and MEP amplitude.

Threshold (rT)

Threshold, as we reported following the guideline of the International Federation of Clinical Neurophysiology (IFCN), is the product of at least 10–20 cortical stimuli at a determined intensity. The evaluation of this parameter in an unstable situation such as sleep can present a methodological problem. Authors have followed different ways to explore rT. Grosse et al. used a stimulus–response paradigm with intensity steps of 4% of maximum output of the stimulator, delivering only three to four magnetic shocks. This procedure is not included in the IFCN recommendations on rT. Grosse et al. evaluated threshold changes between wakefulness and non rapid eye movement sleep stage 2 (NREM2), non rapid eye movement sleep stage 4 (NREM4) and REM sleep, observing an increase of threshold in all sleep stages, more evident in NREM2. This result was confirmed by the same group in a recent paper.

Bertini et al. used a different approach starting from the observation that after awakening, a full re-establishment of regional brain activity pattern needs up to 30 min. They studied, following IFCN guidelines, the relaxed motor threshold in presleep wakefulness, then on awakening from NREM2 and

### Table 1  Effects of the sleep stages on the main conventional single and paired TMS variables in normal subjects.

<table>
<thead>
<tr>
<th>Authors</th>
<th>NREM1</th>
<th>NREM2</th>
<th>NREM3</th>
<th>NREM4</th>
<th>REM</th>
<th>NREM</th>
</tr>
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<tr>
<td>Hess et al.</td>
<td>–</td>
<td>↓ MEP amplitude</td>
<td>–</td>
<td>–</td>
<td>↑/= MEP amplitude</td>
<td>↓ MEP amplitude</td>
</tr>
<tr>
<td>Stalder et al.</td>
<td>–</td>
<td>↓ MEP amplitude</td>
<td>–</td>
<td>–</td>
<td>↑/= MEP amplitude</td>
<td>↓ MEP amplitude</td>
</tr>
<tr>
<td>Goose et al.</td>
<td>–</td>
<td>↑ rT; ↓ MEP amplitude</td>
<td>–</td>
<td>↑ rT; ↓ MEP amplitude</td>
<td>↑ rT; ↓ MEP amplitude</td>
<td>↑ rT; ↓ MEP amplitude</td>
</tr>
<tr>
<td>Manganotti et al.</td>
<td>↓ MEP amplitude</td>
<td>↓ MEP amplitude</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓ MEP amplitude</td>
</tr>
<tr>
<td>De Gennaro et al.</td>
<td>–</td>
<td>=ICF; =ICI</td>
<td>=ICF; =ICI</td>
<td>=ICF; =ICI</td>
<td>=ICF; =ICI</td>
<td>=ICF; =ICI</td>
</tr>
<tr>
<td>Bertini et al.</td>
<td>–</td>
<td>↑ rT</td>
<td>–</td>
<td>–</td>
<td>↑ rT</td>
<td>↑ rT</td>
</tr>
<tr>
<td>Bertini et al.</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>TCI</td>
</tr>
<tr>
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<td>–</td>
<td>=ICF; =ICI</td>
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<td>No ICF; =ICI</td>
<td>=ICF; =↑↑ IC</td>
</tr>
<tr>
<td>Mehrini et al.</td>
<td>–</td>
<td>–</td>
<td>↓ MEP amplitude</td>
<td>↓ MEP amplitude</td>
<td>↓ MEP amplitude</td>
<td>↓ MEP amplitude</td>
</tr>
</tbody>
</table>

**CMCT:** central motor conduction time; **CSP:** central silent period; **MEP:** motor evoked potential; **ICF:** intra–cortical facilitation; **ICI:** intracortical inhibition; **rT:** relaxed threshold; **TCI:** transcallosal inhibition; **TMS:** transcranial magnetic stimulation; **=:** unchanged; **↑:** increase; **↓:** decrease.

* Upon awakening studies.
REM sleep. They observed a linear increase of rT in both awakening stages more evident in NREM2. De Gennaro et al. confirmed a significant change in rT only in NREM state.

Central motor conduction time
During sleep, MEP latency changes linearly with MEP amplitude, as happens in wake. Moreover, CMCT does not show significant differences between wakefulness and sleep. Thus, TMS activates in sleep the same fast-conduction corticospinal fibers as happens in wake.

Motor evoked potential amplitude and stimulus-response curve
The comparison of MEP amplitude in different stages of sleep represents the first attempt to evaluate the modulation of corticospinal excitability during sleep. Hess et al. in 1987 compared motor responses, evoked during sleep, using identical stimuli to those used in wakefulness. The MEP amplitude was depressed during NREM and enhanced or unchanged in REM sleep, suggesting that the susceptibility of the human motor cortex to stimulation is enhanced during REM sleep. Unfortunately this result was not confirmed in a second report. Moreover in different muscles (abductor digiti minimi, lumbar erector spinae, trapezius, and diaphragm), the amplitudes of MEPs were extremely variable as compared to wakefulness and there was no systematic difference among them. Particularly, in NREM sleep a depression of MEP amplitude was observed with respect to REM sleep, with a smaller variability of the responses. In addition, no differences were found in TMS responses between phasic and tonic REM events although MEPs were extremely variable in amplitude. As a likely explanation, the authors suggested that cortical excitability and/or the spinal inhibition fluctuate during REM sleep. New recent data on hand and diaphragm muscles, pointed at a constant reduction of MEPs amplitude during sleep in both muscles without significant effect of sleep stages. Grosse et al. observed during sleep, using a stimulus-response paradigm a flattening of the curve in all sleep stages: NREM2, NREM4 and REM. The reduction of cortical excitability in NREM2 was the most striking effect. In light sleep (NREM1 and NREM2), depression of cortical excitability was also reported.

Paired-pulse transcranial magnetic stimulation
Sleep studies with paired-pulse TMS dealt with intracortical excitability at short interstimulus intervals (ISIs).

![Figure 1](image)

**Figure 1** Different TMS (transcranial magnetic stimulation) approaches in sleep studies. Panel A: SICI (short-interval intracortical inhibition) (ISI 3 ms) and SICF (short-interval intracortical facilitation) (ISI 10 ms) in sleep compared to wakefulness in a single subject. Averaged MEPs (motor evoked potentials) of eight test stimuli, eight conditioned stimuli for all four states of vigilance. The amplitude of test stimulus is kept constant across the different sleep stages and in wakefulness. In NREM 3/4 sleep, there is a marked enhancement of SICI, while ICF (intra-cortical facilitation) is absent in REM sleep. Reproduced with permission from Salih et al. Panel B: Upon awakening paradigm. SICI and ICF in wakefulness and upon NREM and REM awakening. In REM awakening ICF is increased, while upon NREM awakening no significant change is observed. SICI is not affected by sleep stages. Reproduced with permission from De Gennaro et al.
Short-interval intracortical inhibition and facilitation
Salih et al. evaluated SICI and SICF in a large number of subjects (n=28), but only 13 were eligible for the study. The other 15 were excluded for excessive variability of MEP amplitude and motor threshold. SICI and SICF were present in NREM sleep, although SICI was more pronounced in NREM3/4 with respect to wakefulness and other sleep stages (Fig. 1, panel A). In REM sleep SICI was preserved while SICF was abolished. In this study, less than 50% of enrolled subjects were eligible because of excessive variability of TMS parameters. De Gennaro et al. by-passed this problem using the previously described ‘upon awakening’ paradigm. They determined SICI and SICF in wakefulness and upon NREM and REM awakening. The authors observed a significant increase of SICF in REM awakening, while SICF was not affected in NREM awakening (Fig. 1, panel B). SICI did not change through the sleep stages.

Transcallosal inhibition
Transcallosal inhibition was similar in wake and on NREM awakening, while it was reduced after awakening from REM sleep. The decrease of transcallosal inhibition was more pronounced for the right-to-left motor cortex. The drop of transcallosal inhibition after awakening from REM sleep represents the first evidence of changes in interhemispheric connectivity mediated by corpus callosum during sleep stages.

Sleep deprivation
Sleep deprivation (SD) has severe effects on human alertness and performance; it represents a powerful activator of seizures in nearly all types of epilepsy. Two works about TMS and SD were published in the middle of 2001. Although they used several parameters to explore motor cortical excitability, the time course of TMS was different: every 4 h during daytime and every 3 h during night-time29 or after 24 h of SD. This latter approach was recently retested.31

Motor threshold
All studies showed an unchanged rT after 24 h of SD although a significant increase of rT was observed at 03.00 and 06.00 a.m.29

Central silent period
Results concerning this variable were controversial. Old studies did not show significant changes of CSP after 24 h of SD although Manganotti et al. observed a significant prolongation of CSP at 03.00 a.m. Recently, Scalise et al. reported a shortening of CSP length after 24 h of SD.

Paired TMS
Twenty-four hours of SD induced heterogeneous effects in the normal subject. Different authors found, respectively: no change of SICI and SICF, decrease of SICI and an increase of SICF. De Gennaro et al. explored, in an interesting study of correlation between TMS and EEG activity, the effects of 48 h of SD. In the normal, they observed an increase of rT and in females only an increase of SICF. These changes were coherent with the increase of theta EEG activity in left and midline frontal and prefrontal regions, observed after SD.

Sleep disease (Table 2)
Among the main entities classified in the sleep disease group, the following were subject to TMS studies: obstructive sleep apnoea syndrome (OSAS), propriospinal myoclonus, restless legs syndrome (RLS) with periodic limb movements, and narcolepsy.

<table>
<thead>
<tr>
<th>Sleep disorder</th>
<th>CMCT</th>
<th>Threshold</th>
<th>MEP amplitude</th>
<th>CSP</th>
<th>SICI</th>
<th>SICF</th>
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<td>OSAS</td>
<td>Normal36,37</td>
<td>Normal36,37</td>
<td>MEP amplitude (NREM)</td>
<td>Prolonged36,37</td>
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<td>–</td>
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<tr>
<td>Propriospinal myoclonus</td>
<td>Normal38</td>
<td>Normal38</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Narcolepsy</td>
<td>Normal47</td>
<td>Increased (rT, aT)47</td>
<td>–</td>
<td>–</td>
<td>Normal47</td>
<td>Increased47</td>
</tr>
</tbody>
</table>

Obstructive sleep apnoea syndrome

Central motor conduction time
Obstructive sleep apnoea syndrome is an insidious condition characterized by repetitive upper airway closure during sleep that includes a constellation of symptoms, commonly excessive daytime somnolence and cognitive defects. Its pathophysiology has not been completely understood yet.34

In a preliminary report, a prolongation of MEP latencies in hand muscles of patients with OSAS was observed.35 The authors suggested a widespread defect in the conductivity or excitability of the corticomotor system.35 Recently, this conduction/excitability defect was not confirmed.36,37

Threshold and central silent period
In OSAS patients, during wake, rT was similar to normal controls,36,37 while the CSP length was increased.36,37

Motor evoked potential amplitude
During wake the mean MEP amplitude was not different between patients and controls.36 In NREM2-sleep we observed a significant reduction of MEP amplitude (50% of awake mean amplitude) (Fig. 2, panels A and B), while in apnoea-NREM2 we observed a dramatic drop of MEP amplitude (10% of awake MEP mean amplitude) (Fig. 2, panels A–C).

We suggested that cortical excitability changes could represent a depression of neuromotor descending drive related to apnoea episodes.36

Propriospinal myoclonus at the sleep–wake transition
Propriospinal myoclonus has been attributed to spinal generators, involving thoracic, paraspinal and in some cases cervical muscles, characterized with a typical recruitment order up and down the spinal cord via slowly conducting pathways. Vetrugno et al.38 recently applied TMS in five patients with propriospinal myoclonus. In the awake state, MEPs were recorded from abductor pollicis brevis and tibialis anterior muscles. TMS parameters (CMCT, rT and aT) were normal.38

Restless legs syndrome
RLS is a sensory-motor disorder characterized by an irresistible urge to move the legs. It is accompanied by uncomfortable sensations that lead to sleep disturbances. The symptoms show a strong circadian rhythmicity, with onset or increase in the evening or at night. Although it has large distribution in the general population, the neural circuitry contributing to RLS remains speculative. A non-specific hyperexcitability of motor neuron

Figure 2  Obstructive sleep apnoea syndrome (OSAS) and transcranial magnetic stimulation (TMS). Panel A: Box plots represent the range of the MEP (motor evoked potential) amplitude values during relaxed wake, stage 2 of non-REM sleep, and an obstructive apnoea in the OSAS patient group. Apnoea values are significantly (*P<0.05) reduced in comparison with both wake and NREM2. Panel B: Box plots represent the range of the MEP latency values during relaxed wake, stage 2 of NREM sleep, and an obstructive apnoea in the OSAS patient group. Apnoea values are significantly (*P<0.05) increased in comparison with both wake and NREM2. Mean values are represented by bold horizontal line. Bars=±S.D. Panel C: Typical examples of the MEP size and latency changes during relaxed wake (W), NREM2 (nR2), and an obstructive apnoea (A) in two OSAS patients. Tracings represent the overlap of 15 MEPs in wake, and 10 in non-REM2/apnoeas. Average SaO2 values (±S.D.) in the three different conditions are also shown. Reproduced with permission from Civardi et al.36.
Circuitries may well correlate with the urge to move the lower limbs. To test this hypothesis, Tergau et al.\textsuperscript{39} used s-TMS and p-TMS in a group of 18 RLS patients. Only p-TMS showed a significant impairment of intracortical inhibition in foot and hand muscles. Instead, intracortical facilitation was decreased in foot but not in hand muscles (Fig. 3, panel A). Thus, the different behaviour of lower limb muscles was attributed to subliminal activation of the corticospinal tract, which would be typical in RLS. Tergau et al.\textsuperscript{39} concluded that RLS is characterized by a dis-inhibition of subcortical centres sending inputs to the motor cortex, without a cortical involvement. These results were later reproduced by two groups.\textsuperscript{40,41} They confirmed that the syndrome core pathophysiology lays in basal ganglia and other subcortical centres controlling the corticospinal outputs. Unfortunately, as in other diseases the CSP showed different behaviour: normal length\textsuperscript{39–41} or markedly reduced length.\textsuperscript{42–44} Reduction was reversed by dopaminergic drugs.\textsuperscript{43}

According to the CSP sensitivity to dopamine modulation and the effectiveness of L-dopa in RLS symptoms, the authors confirmed the potential key role of basal ganglia in RLS pathophysiology.\textsuperscript{42–44} Cabergoline (Fig. 3, panel B) also normalized p-TMS.\textsuperscript{41,44}

Although no details on the study method were provided, in RLS patients with periodic limb movements, TMS was 'normal'.\textsuperscript{45} Moreover, Scalise et al.\textsuperscript{46} proposed an alteration/reduction in central plasticity without clarifying if cortical changes are the effect of basal ganglia abnormalities or the disease marker.

In all studies RLS patients were studied on awakening. Although with somewhat contradictory findings, probably due to the different timings, they showed a reduction of SICI and a decrease of CSP length, pointing to a derangement of basal ganglia control on to the primary motor cortex.

**Figure 3** Restless legs syndrome (RLS) and transcranial magnetic stimulation (TMS). Panel A: In RLS TMS shows a significant impairment of SICI (short interval intracortical inhibition) when recording from foot and hand muscles, while SICF (short-interval intracortical facilitation) is decreased in foot but not in hand muscles. Mean values of RLS patients and control subjects as obtained by the paired conditioning-test-stimulus paradigm. Results for the abductor digiti minimi (plotted on the left) and abductor hallucis (plotted at the right) muscles. The conditioned MEP size after p-TMS (paired pulse TMS) is expressed on the ordinate as a percentage of the unconditioned MEP (motor evoked potential) size. RLS patients (black dots) and control subjects (white dots). The abscissa indicates the interval (in milliseconds) between the conditioning and the test stimulus. Error bars indicate S.D. *Student’s t-test P < 0.05 when tested against control group. Reproduced with permission from Tergau et al.\textsuperscript{39}. Panel B: Effects of cabergoline treatment on short-interval intracortical inhibition: histogram shows mean values (average of ISIs 1, 3, 5 ms) for SICI in RLS patients and in control subjects, before (grey bars) and after (black bars) cabergoline treatment; error bars are S.D. Reproduced with permission from Nardone et al.\textsuperscript{41}.
Narcolepsy

Narcolepsy is a syndrome characterized by excessive daytime sleepiness, hypnagogic hallucinations, cataplexy, sleep paralysis and sleep fragmentation. In a single patient, during cataplexy, TMS did not show differences (in comparison with the normal state) in rT and corticospinal excitability. Recently, in narcoleptic patients (Fig. 4) s-TMS, performed on awakening, showed a significant increase of rT and aT, while CSP and CMCT were unaffected. Paired TMS showed a significant increase of SICI. Thus, changes in excitability of intrinsic circuits in motor cortex, observed in narcolepsy, could correlate with the deficit of hypocretin/orexin system, through a reduction of histaminergic hypothalamic inhibitory projections to cortical GABAergic neurons.

Repetitive transcranial magnetic stimulation as a diagnostic tool

Trains of 20-Hz rTMS at 1.1×rT for 2 s were able, only in narcoleptic patients (3 pts), to induce a prolonged suppression of voluntary first dorsal interosseous muscle contractions lasting from 0.6 to 3.5 s. This effect was suppressed by anti-cataplectic therapy. The authors proposed rTMS as an additional method to diagnose narcolepsy. Shorter trains—1.5 s—produced less significant voluntary muscle suppression.

Repetitive transcranial magnetic stimulation as a therapeutic tool

Potential therapeutic effects of rTMS in sleep came firstly from the analogy of TMS with electroconvulsive therapy in depressed patients. Patients with major depression showed a reduction of REM latency. Cohrs et al. tested the effects of a high frequency (20 Hz) active and sham rTMS in normal subjects. Active rTMS induced a significant prolongation of REM latency compared to the sham stimulation. This effect was more evident for

Repetitive-pulse transcranial magnetic stimulation in sleep

Repetitive-TMS represent a new interesting tool in sleep medicine. Combining rTMS with high-density EEG showed new perspectives in sleep.
the left prefrontal cortex stimulation. In a crossover study, Graft et al.\textsuperscript{54} compared the effects of real versus sham rTMS applied in the left dorso-lateral prefrontal cortex (DLPFC) in eight normal subjects. They delivered 40 trains at 20 Hz of 2-s durations at 0.9\texttimes rT. They observed a small reduction of NREM1 over the whole night and a small enhancement of NREM4 without changing the topography of EEG power spectra in the all-night sleep registration.

The antidepressant protocol of rTMS induced small\textsuperscript{54} or null\textsuperscript{55} effects on sleep. Other studies showed that rTMS increases antidepressant effects of sleep deprivation.\textsuperscript{56,57}

Two patients with primary chronic insomnia were treated with rTMS.\textsuperscript{58} They received two different rTMS sections (10 and 1 Hz) over the left DLPFC, reporting sleep improvement. This was reflected by a reduction of sleep latency, an increase in total sleep time and REM sleep latency.

All the reported studies showed very weak clinical effects and the improvement of sleep architecture may be secondary to the (temporary) relief of the psychiatric symptoms. This supports the idea of rTMS as a psychiatric therapy more than a primary sleep therapy.

Repetitive transcranial magnetic stimulation combined with EEG

In the past 3 years, a new way of combining TMS and EEG provided new perspectives in sleep study. TMS can activate the human brain in a safe and non-invasive way, while surface potentials of extracellular population can be recorded using EEG to provide direct means of cortical responses to stimulation.\textsuperscript{59} In wakefulness,\textsuperscript{60} a slow rTMS train (about 0.5 Hz) applied to the rostral portion of the right premotor cortex induced EEG changes in frontal, premotor and motor area bilaterally. During NREM sleep, TMS—EEG changes were confined to the site of stimulus through the breakdown of transcallosal and long-range connectivity.\textsuperscript{60} Realistic electrode positions were obtained using MRI scans. The authors digitized and coregistered for each subject electrode positions and then they constructed a realistic head model.\textsuperscript{60–62} The same authors performed two other studies.\textsuperscript{61,62} During sleep they observed that rTMS can enhance the activity of a fundamental sleep rhythm, called 'slow wave EEG activity' (SWA). SWA is a more sensitive indicator of an efficient sleep activity, and has been shown to correlate with synaptic plasticity, learning, and it was found reduced in subjects affected by sleep disorders. This finding suggested that rTMS can induce plastic changes (long term potential (LTP)-like effects) and improve the quality of sleep. Potentiation occurs distant from the site of stimulation and to a larger extent than where stimulation is delivered. This way to combine TMS and EEG gives new and intriguing information helpful to localize potential cortical target of rTMS treatment to induce an increase of SWA. The technique presented here can be used to assess whether potentiation or depression is induced and which are the cortical areas involved.

Practice points

1. TMS represents a new and complementary approach in the study of sleep pathophysiology. This technique represents a safe and painless tool for assessing the functional changes in motor cortical output, in sleep and its disease.
2. The main limit of TMS application in this field, is its acoustic interference with the sleep structure. In fact the discharge of the capacitors produces a loud sound able to awake subjects or lighten their sleep.
3. In sleep disorders TMS showed interesting data, although sometimes contrasting, because of a few number of subjects, therefore it should be required multi-centre studies to increase the population sample.
4. The use of rTMS as a potential tool to reverse / relieve defects in cortical function, opens new perspectives in the therapeutic area of sleep disorders.
5. At the moment, TMS is a useful technique in sleep research. However, interesting applications are expected in the clinical practice too.

Research agenda

1. TMS studies in sleep should be applied to larger homogeneous and clinically classified populations.
2. TMS research will deal with important sleep-related issues such as consciousness and drugs mechanism of actions.
3. The combined use of TMS with advanced EEG techniques, fMRI or PET is the next perspective.
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References

* The most important references are denoted by an asterisk.


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