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Original Article

Direct comparison of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome and restless legs syndrome

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ABSTRACT

Objective: Changes to transcranial magnetic stimulation (TMS) have been reported in obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS), although no direct comparison study is available. The aim of this new investigation is to assess and compare cortical excitability of OSAS and RLS patients using the same methodology and under the same experimental conditions.
Methods: Fourteen patients with OSAS and 12 with RLS were compared to 14 age-matched controls. All patients were untreated and had a severe degree of disease. Resting motor threshold (rMT), cortical silent period (CSP) and motor evoked potentials MEPs, as well as intracortical inhibition (ICI) and facilitation at interstimulus interval (ISI) of 3 and 10 ms, respectively, were explored from the right first dorsal interosseous muscle, during wakefulness.
Results: rMT was higher in OSAS than in RLS and controls. CSP was shorter in RLS only when compared to apneic patients, whereas it was similar between OSAS and controls. OSAS subjects exhibited slightly prolonged central motor conductivity, whereas MEP amplitude was smaller in both patient groups. The ICI ratio at ISI of 3 ms was decreased in RLS patients only.
Conclusions: Distinct changes of responses at TMS were found, probably connected with the different neurophysiological substrates underlying OSAS and RLS and could not be interpreted as a mere reflection of the effects of sleep architecture alteration. TMS can be considered an additional tool for the understanding of clinical and pathophysiological aspects of sleep disorders, and possibly for the evaluation of the effect of therapy.

1. Introduction

In the last years, several studies have been carried out to evaluate the neurophysiological pattern of cortical excitability to transcranial magnetic stimulation (TMS) in different sleep disorders, including obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS), based on evidence suggesting that there might be a transient modified global excitability of the cortical-spinal pathways in some sleep disorders[1–3]. A number of TMS studies have confirmed that the cortical silent period (CSP) was prolonged in OSAS patients [4–7], as a sign of an increase in gamma-aminobutyric acid (GABA)-B activity [8]. On the contrary, the dysfunction of subcortical structures in RLS might induce a cortical disinhibition [9] and an alteration in cortical plasticity [10], both of which are likely to be modulated by dopaminergic drugs [11,12]. However, although the findings from these reports seem to reveal substantial modifications of the cortical excitability compared to healthy good sleepers, the complexity and heterogeneity of sleep disorders, the relatively low number of investigations and the heterogeneity in the methods employed preclude a comprehensive understanding [13]. In particular, studies assessing whether these changes might be related to the underlying specific pathophysiological mechanisms of the different sleep disorders or they merely reflect a general effect of disturbed nocturnal sleep are missing. Moreover, to date no investigation aiming to a direct TMS comparison between OSAS and RLS patients has been conducted.

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TMS is a safe, non-invasive, and painless tool by which hypotheses regarding cortical excitability can be explored *in vivo* in humans. TMS allows the examination of the descending motor pathways, from the motor cortex down to the target muscles [14]. Different paradigms of stimulation can be applied to obtain direct measures of cortical excitability and can also be indirectly used to detect information regarding the function of various neurotransmission systems [15], providing insights into the complex pathophysiology of a number of psychiatric and neurological conditions. Several variables, such as the threshold to stimulation at rest (resting motor threshold, rMT), the motor evoked potentials (MEPs), the central motor conduction time (CMCT), and the CSP may be assessed by means of the single pulse technique. Additionally, the paired-pulse method allows the measurement of the intracortical inhibition (ICI) and intracortical facilitation (ICF) [16], that likely reflects the excitability of separate populations of intrinsic interneurons within the motor cortical areas [17].

The aim of this new study is to use these methods in order to detect any changes in the electrocortical excitability of patients with OSAS and RLS, both compared with age-matched controls, using the same methodology and TMS procedures for all participants as well as the same experimental conditions. Based on the heterogeneous data collected in our recent review on this matter [13], we hypothesized that changes to TMS in OSAS and RLS might represent disease-specific profiles rather than a general consequence of the sleep architecture alteration.

2. Methods

2.1. Subjects and assessment

Fourteen patients with OSAS (8 males and 6 females; mean age, 57.9 ± 6.02 years), 12 patients with RLS (4 males and 8 females; mean age, 61.7 ± 11.44) and 14 age-matched controls (5 males and 9 females; mean age, 64.4 ± 5.37 years) were consecutively recruited from the Sleep Research Centre of the "Oasi Institute for Research on Mental Retardation and Brain Aging", Troina (Italy). OSAS patients met the international diagnostic criteria [18], and their clinical-polysomnographic findings were concordant with a severe disease. Subjective sleepiness, assessed by the Epworth Sleepiness Scale (ESS), was relevant (average score 16 ± 4.96 S.D.) and nocturnal snoring was always reported; mean oxygen desaturation index (defined as the number of peripheral blood oxygen desaturation per hour >3% from baseline) was 59.9 ± 27.07 S.D. The participants with RLS fulfilled the latest International Restless Legs Syndrome Study Group diagnostic criteria [19], and their mean score at the International Restless Legs Syndrome Study Group rating scale [20] was compatible with a severe disease (25.3 ± 4.89 S.D.); their mean EES score was 12.8 ± 3.44 S.D.

The clinical-demographic evaluation included: age, gender, handedness, social and living conditions, general and neurological examinations, and co-morbidities. The right handedness of all individuals was checked with the Edinburgh Handedness Inventory [21]. None of the patients was treated, neither with continuous positive airway pressure (CPAP) nor with drugs for RLS.

Exclusion criteria were: age <18 years; history of major psychiatric illness or other neurological disorders (ie, Parkinson's disease, epilepsy, stroke, dementia, head trauma, multiple sclerosis, etc.); other sleep disorders, such as abnormal sleep–wake rhythm, insomnia, narcolepsy; previous treatment with CPAP or dopaminergic drugs; acute or chronic non-compensated medical illness, including chronic obstructive pulmonary disease; alcohol/illicit drug abuse; current intake of psychoactive medications or other drugs able to modulate cortical excitability (ie, steroids, beta-blockers, clonidine, etc.); Mini Mental State Examination [22] <24; any conditions precluding TMS execution. Electroencephalography (EEG) was performed to rule out predisposition to seizures. In addition, to rule out a possible spinal or peripheral contribution to the motor cortex excitability parameters, a routine conduction study of the right ulnar nerve, including the F-waves, was performed prior to the entry into the study; this was found to be normal in all patients.

The study was approved by the local Ethics Committee and all subjects gave their written informed consent prior to the study after full explanation of the procedure.

2.2. Transcranial magnetic stimulation

TMS was performed using a high-power Magstim 200^2 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). A 70 mm figure-of-eight coil was held over the motor cortex at the optimum scalp position to elicit MEPs in the contralateral First Dorsal Interosseous (FDI) muscle of the dominant hand. The rMT was defined as the lowest stimulus intensity able to elicit MEPs at rest of an amplitude >50 μV in at least 5 of 10 trials, according to the IFCN recommendation [23]. CMCT was calculated by subtracting the conduction time in peripheral nerves obtained by magnetic stimulation of the cervical root, from the MEP cortical latency obtained during moderate active muscle contraction, with a stimulus intensity set at 130% of the rMT. The CSP was determined with an approximately 50% of maximum tonic voluntary contraction of the FDI muscle, induced by single TMS pulses delivered at 130% of rMT. The mean CSP duration of 10 rectified trials was calculated.

Paired-pulse TMS was performed using a 70-mm figure-of-eight coil deriving pulses from a couple of Magstim 200^2 Stimulators, connected each other through a BiStim module (The Magstim Company, Whitland, Dyfed). The BiStim was connected to a CED Micro 1401 interface (Cambridge Electronic Design, Cambridge, UK) allowing stimulus generation and data capture. ICI and ICF were studied using the conditioning-test paradigm, applying two magnetic stimuli in rapid succession [16]. The conditioning stimulus was set at 80% of the subjects' rMT whereas the test stimulus was set at 130% of the rMT. The interstimulus intervals (ISIs) tested were 3 and 10 ms, given that maximum inhibitory effects are found at short ISIs (1–4 ms) whereas facilitatory effects can be observed at longer intervals (7–20 ms) [14]. Ten trials for both ISIs were recorded in a random way with an 8-s interval among each trial. Responses were expressed as the ratio between the MEP amplitude produced by paired stimulation and that produced by test stimulus alone. Data were collected on a computer and stored with software *ad hoc* for off-line analysis [24].

Electromyographic (EMG) activity was recorded with silver/silver-chloride disposable self-adhesive and self-conductive surface electrodes. The active electrode was placed over the muscular belly of the target muscle (FDI), the reference distally at the metacarpal-phalangeal joint of the index finger and the ground on the dorsal face of the wrist. All measurements were conducted while subjects were seated in a comfortable chair with continuous EMG monitoring to ensure either a constant level of muscular activity during tonic contraction or complete relaxation at rest. All procedures were performed in the same laboratory and situation, by the same operators for each subject during wakefulness and at the same time of the day (approximately 9–10 am).

The level of vigilance of apneic patients was constantly checked throughout the experiment and kept to an acceptable level by asking the subject the number of the current trial prior to the administration of each TMS pulse.

2.3. Statistical analysis

The comparison between the different parameters obtained in the three groups of subjects was carried out by means of the non-parametric Kruskal–Wallis ANOVA, followed by the Mann–Whitney

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