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Editorial

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Transcraníal Magnetic Stimulation for Restless Legs Syndrome: Probing the Neurophysiological Basis towards a Novel Therapeutic Tool?

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Abbreviations: EEG: Electroencephalography; RLS: Restless Legs Syndrome; TMS: Transcranial Magnetic Stimulation; rTms: Repetitive Transcranial Magnetic Stimulation

Studies using Trancranial Magnetic Stimulation (TMS), a noninvasive neurophysiological technique assessing the excitability of motor cortical areas and their projections, have revealed cortical and cortical-spinal dysfunction in several sleep disorders. In particular, cortical hyper excitability has been observed in several studies in Restless Legs Syndrome (RLS) and seems to reflect a disease-specific profile rather than a general consequence of sleep architecture alteration [1]. The repetitive TMS (rTMS) paradigm is known to be able to transiently modulate the excitability of the stimulated area, mostly depending on the frequency of stimulation, usually being

the high-frequency stimulation excitatory and the low-frequency stimulation inhibitory. In this context, the literature on the neurophysiological basis underlying RLS is not conclusive and, to our knowledge, only one preliminary study has been performed on the potential efficacy of high-frequency rTMS in RLS patients [2].

We have very recently carried-out an extensive review of the literature concerning the use of TMS in sleep disorders [1] showing that, even considering the high heterogeneity of the data reported by the different studies, RLS seems to be characterized by a specific pattern of abnormalities at TMS that points at a reduced motor cortex excitability and abnormal motor cortex plasticity phenomena. In order to overcome the heterogeneity of the data collected earlier, we have also run a direct comparison study not only between RLS patients and healthy controls but have also included patients with obstructive sleep apnea syndrome; the study [3] fully confirmed the indirect comparisons carried out with the earlier review. Another recent study using Electroencephalography (EEG) during the sleep onset period in RLS patients compared to controls and to insomniacs [4] allowed to demonstrate that increased EEG alpha and beta bands are present in RLS versus normal controls, during both wakefulness preceding sleep and the sleep onset period, supporting the hypothesis of the presence of a state of hyper arousal in RLS during the sleep onset period which might represent a good target of specific treatment. Based on these findings and those from previous studies, we know that RLS

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patients exhibit an overall pattern of "disinhibition" to TMS, thus resulting in a hyper excitability state of the motor cortical areas.

In this context, we hypothesize that low-frequency (inhibitory) rTMS of the primary motor cortex might be more beneficial than high-frequency in RLS patients, whose motor areas and cortical-spinal system are hyper excitable. As a support for this hypothesis, it is also known that rTMS induces dopamine release in the basal ganglia [5] and that dopamine-agonists are the current first line drugs for RLS, although some patients complain incomplete response.

Possible critical aspects of the application of TMS in patients with RLS include the following: a) TMS-related measures of cortical excitability do not provide specific pathophysiological information but are sensitive to the "global weight" of several neurotransmitters as well as subcortical and cortical motor inputs; therefore, TMS might provide further insight on the neurochemical mechanisms underlying RLS; b) the hypothesis to identify a characteristic signature in patients with RLS could be risky given the lack of previous data and the difficulty of similar approaches in other sleep disorders; c) most of the previous studies have been performed in the awake state, and thus in a condition different from sleep; d) the use of a hand muscle in RLS subjects might not be adequate, although some TMS measures have shown to be involved even when recording over hand muscles [6].

In conclusion, probing the effects of TMS on motor or sensory disturbances often complained by RLS patients may prove a powerful tool for a novel experimental treatment. If this hypothesis provides valuable information at the individual level, TMS, integrated with clinical, hypnologic and advanced neuroimaging data, might prompt a design of an instrument for the neurophysiological study of RLS and other sleep disorders and for an innovative non-pharmacological approach.

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