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Review Article

Central and peripheral nervous system excitability in restless legs syndrome

Giuseppe Lanza [a, *], Cornelius G. Bachmann [b], Imad Ghorayeb [c, d], Yuping Wang [e], Raffale Ferri [a], Walter Paulus [f]

[a] Sleep Research Center, I.R.C.C.S. "Oasi Maria SS.", Troina, Italy
[b] Department of Neurology, Paracelsus Klinik, Osnabrueck, Germany
[c] Department of Clinical Neurophysiology, CHU de Bordeaux, Bordeaux, France
[d] CNRS, INCIA, CNRS UMR 5287, Université de Bordeaux, Bordeaux, France
[e] Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China
[f] Department of Clinical Neurophysiology, University Medical Center, Georg August University Göttingen, Göttingen, Germany

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ABSTRACT

Neurophysiological techniques have been applied in restless legs syndrome (RLS) to obtain direct and indirect measures of central and peripheral nervous system excitability, as well as to probe different neurotransmission pathways. Data converge on the hypothesis that, from a pure electrophysiological perspective, RLS should be regarded as a complex sensorimotor disorder in which cortical, subcortical, spinal cord, and peripheral nerve generators are all involved in a network disorder, resulting in an enhanced excitability and/or decreased inhibition. Although the spinal component may have dominated in neurophysiological assessment, possibly because of better accessibility compared to the brainstem or cerebral components of a hypothetical dysfunction of the diencephalic A11 area, multiple mechanisms, such as reduced central inhibition and abnormal peripheral nerve function, contribute to the pathogenesis of RLS similarly to some chronic pain conditions. Dopamine transmission dysfunction, either primary or triggered by low iron and ferritin concentrations, may also bridge the gap between RLS and chronic pain entities. Further support of disturbed central and peripheral excitability in RLS is provided by the effectiveness of nonpharmacological tools, such as repetitive transcranial magnetic stimulation and transcutaneous spinal direct current stimulation, in transiently modulating neural excitability, thereby extending the therapeutic repertoire. Understanding the complex interaction of central and peripheral neuronal circuits in generating the symptoms of RLS is mandatory for a better refinement of its therapeutic support.

1. Introduction

The pathophysiology of restless legs syndrome (RLS) might be seen as a continuous spectrum, with a major genetic contribution at one end and a major environmental or co-morbid disease contribution at the other [1]. Although the dopaminergic link is yet to be supported by genetics, dopaminergic pathways have been suspected playing a central role, because RLS symptoms improve under low-dose dopaminergic substitution therapy and worsen under neuroleptic drugs [2,3]. However, to date, the anatomical location of the dopaminergic dysfunction is still a matter of debate. Dysfunction of the A11 diencephalic DOPAergic system has been postulated in animal models, given that this area is the main source of dopaminergic innervation for the spinal cord [4–6]. However, an autopsy study failed to demonstrate any pathologic change in the A11 region in humans [7]. It is also likely that the dopaminergic dysfunction is linked to changes in iron metabolism within the brain. This is supported by reduced deposits of iron in the substantia nigra and low ferritin levels in the blood and cerebrospinal fluid (CSF) of some RLS patients [8–12]. In addition, experimental evidence in iron-depleted animals shows that disruption in brain iron homeostasis leads to disturbances in dopamine neurotransmission in multiple brain areas [13,14]. Furthermore, low ferritin

* Corresponding author. Sleep Research Center, I.R.C.C.S. "Oasi Maria SS.", Via Conte Ruggero 73, 94018 Troina, Italy. Fax: +39 0935 936694.
E-mail address: glanza@oasi.en.it (G. Lanza).

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serum concentration is a risk factor for the so-called augmentation, a worsening of symptoms under dopaminergic therapy.

Interestingly, recent lines of evidence suggest a more widespread cerebral involvement, affecting personality traits [15,16], mood regulation [17], functional thalamus–cortical connectivity [18], and cortical–spinal excitability [19]. In this context, a number of electrophysiological methods have been applied in RLS to obtain direct and indirect measures of cortical and spinal excitability. This has allowed exploring the neurophysiological basis underlying the syndrome, probing the functioning of different neurotransmission pathways, and paving the way for an enlargement of the therapeutic arsenal on a more rational basis.

In this review, we provide a comprehensive perspective of current research on cortical, spinal, and peripheral nerve excitability in RLS to gain further insights into the neurophysiology and pathophysiology of the syndrome, and to help guide future studies. To identify the studies available on RLS neurophysiology, a PubMed-based literature search was conducted. The following data were considered: (1) study design; (2) sample characteristics, such as the number of participants, age, sex, presence/absence of treatment, time of the day, wakefulness/sleep state; (3) neurophysiological method used and its technical features; (4) results; and (5) limitations. A hand search was also performed on the retrieved articles to identify additional data.

2. Neuronal excitability in RLS

2.1. Cortical excitability and brainstem reflexes

Pathological excitability of cortical neurons to transcranial magnetic stimulation (TMS) has been proposed as a candidate mechanism, thereby supporting the hypothesis of a motor cortex dysfunction in RLS pathogenesis [20,21]. TMS is a painless and noninvasive neurophysiological technique capable of assessing the primary motor cortex (M1) and cortical–spinal tract excitability in vivo. Stimulation of the M1 generates motor evoked potentials (MEPs) in contralateral muscles that can be registered by surface electromyography, thus providing relevant information about the excitability of motor cortical areas and cortical–spinal conductivity in healthy subjects and in patients with a variety of neurological and psychiatric disorders [22–24].

Table 1 summarizes the literature on TMS studies carried out in RLS patients. Although the studies conducted so far are methodologically heterogeneous, especially regarding the stimulation protocols and the characterization of subjects (ie, disease severity, timing of experiments, use of drugs, level of vigilance, and quality of sleep the night before), overall they support the hypothesis that RLS may be caused by, or may lead to, a pathologically enhanced excitability of cortical neurons [20,21]. Hyperexcitability in these studies may be due to an impairment of intracortical inhibitory circuits, as shown by a significant decrease of cortical silent period (CSP) and short-latency intracortical inhibition. These parameters are considered as neurochemical signs of intracortical γ-aminobutyric acid (GABA) activity. However, they are also likely to be comodulated by dopaminergic drugs, given that a "restoration" to the level of healthy controls is reported by several investigations under dopaminergic substitution (for recent comprehensive reviews, see Lanza et al. [20] and Magalhães et al. [21]).

A circadian loss of cortical inhibition was also observed, with a CSP tendency to shorten at night [38]. Conversely, resting motor threshold and MEP amplitude were not significantly different between RLS patients and controls [26,30], although active motor threshold was significantly lower in the RLS group during the nighttime, suggesting a global enhancement of M1 excitability [38]. It is unclear whether this electrocortical pattern is specific to RLS, as it also reflects the behavior under preactivation of muscles. However, this TMS profile is different from that reported in other sleep disorders, such as obstructive sleep apnea syndrome, insomnia, and experimentally induced sleep deprivation, making unlikely the hypothesis that it reflects the general impact of sleep architecture alteration [39]. A global hypoexcitability of the M1 and cortical–-spinal neurons might be a feature of apneic patients; results on insomniac or sleep-deprived subjects underline an intracortical inhibitory/excitatory imbalance, often in favor of an "activating" pattern [20].

Associative sensorimotor interaction and measures of cortical plasticity have been shown to be also affected in RLS. A study aiming at the evaluation of changes of motor cortex excitability occurring at different timings after a repetitive bimanual finger movement task did not show the normal fluctuations of the MEPs amplitude [29,30]. In normal subjects, indeed, MEP size increased both immediately after exercise (postexercise facilitation) [40,41] and after rest (delayed facilitation) [42]. Postexercise facilitation is thought to be due to increased excitability of the motor cortex [40,41]; delayed facilitation likely reflects intracortical synaptic reorganization consequent to repetitive motor tasks, suggesting phenomena of cortical plasticity [42–45]. The lack of significant amplitude changes in RLS patients, both after exercise and after rest, suggests an abnormal pattern of cortical plasticity/motor learning as an effect of repetitive exercise [29,30]. Paired associative stimulation (PAS), a protocol performed by coupling electrical peripheral nerve stimulation with TMS, which normally showed increased cortical–spinal excitability in healthy subjects, was not changed in idiopathic RLS [34]. Some of these abnormalities are reversible under therapy: pramipexole increased central motor inhibition [27,31–33,35,36]; PAS-induced plasticity could be restored after four weeks of dopaminergic treatment [34].

Finally, several studies assessing sensorimotor integration in RLS with reflex tasks showed ambiguous results. Blink reflex responses were reported to be normal in RLS patients [46]. Consistent with this finding, the effect of auditory stimuli and tactile lower limb stimulation as prepulse conditions on the R2 response of the blink reflex were not different between RLS patients and matched controls [47]. However, a study investigating sensorimotor interaction using eyeblink reflex conditioning with auditory stimuli, either paired or not paired with an airpuff unconditioned stimulus, even showed deficits in RLS patients [48]. In contrast, the acoustic startle reflex, as a brainstem reflex elicited by an unexpected noisy stimulus, was significantly more frequent and with a shorter latency in RLS patients, supposedly indicating disinhibited reticular–spinal pathways [49].

2.2. Spinal excitability

We currently understand RLS as a network disorder that includes the spinal cord in its pathogenesis [50]. Indeed, spinal hyperexcitability during the symptomatic period, reversed by dopaminergic treatment, was demonstrated in several studies [51,52]. Interestingly, the spinal cord, deprived of its cortical influence, is able to generate similar rhythms as compared to periodic limb movements (PLMs), although without circadian changes [53]. Involuntary leg movements of some patients with complete transection of the spinal cord are also identical to PLMs in RLS [54–56].

Painful symptoms in RLS and several chronic pain conditions further link RLS to the spinal cord, as several pain neuromodulators (mainly serotonin, norepinephrine, dopamine, acetylcholine, and opioids) are involved in both RLS and pain control ([57,58]; for an overview, see Millan et al. [59]). Several studies showed an increased prevalence of RLS in different chronic pain conditions, such as fibromyalgia (23%) [60], neuropathic pain (40%) [61],