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Original Article

Connecting clinical aspects to corticomotor excitability in restless legs syndrome: a TMS study

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ABSTRACT

We assessed corticomotor excitability in the primary motor cortex (M1) of participants with moderate-to-severe restless legs syndrome (RLS) symptoms using transcranial magnetic stimulation (TMS) in relation to the clinical and sleep aspects of the disease. Thirty-five participants (20 F; mean age: 59.23 ± 1.66 years; range: 42–78 years) affected by primary RLS (off medications) and 31 age-matched controls (19 F; mean age: 57.90 ± 1.50 years; range: 43–79 years) underwent TMS following two nights of polysomnography (PSG). Paired-pulse TMS measures [short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and intracortical facilitation (ICF)] of the dominant $M1_{hand}$ and $M1_{leg}$ muscles were collected and analyzed in relation to clinical features of RLS and PSG. We found decreased corticomotor excitability in $M1_{hand}$, whereas it was increased in $M1_{leg}$, which was greater in patients with more severe RLS. Participants with RLS with a history of dopamine-agonist–induced symptom augmentation showed decreased LICI (reduced inhibition) compared to nonaugmented participants with RLS for $M1_{leg}$. None of the TMS measures ($M1_{hand}$ or $M1_{leg}$) correlated with the PSG parameters. This study shows hyperexcitability in $M1_{leg}$, and this appears related to RLS disease severity and decreased excitability in $M1_{hand}$. The results provide new insight into the complex neurobiology of RLS, particularly in more advanced stages of the disease.

1. Introduction

More than six million Americans suffer from moderate-to-severe restless legs syndrome (RLS). Many of these individuals report significant disability, reduced work productivity, diminished quality of life, and increased depression and anxiety [1–4]. Clinical studies have reported that patients with RLS have a greater sustained alertness than expected for their degree of sleep loss [5]. This clinical feature is more or less similar to what has been postulated to underlie primary insomnia, where the term “hyperarousal” has been used to describe the increased wake time during the night without significant symptoms of daytime sleepiness. To date, RLS research has primarily focused on leg symptoms and movements and ignored the major RLS feature “hyperarousal” that may actually drive the primary symptoms [4].

Notably, RLS has been shown to be associated with increased excitability and reduced inhibition at different levels within the nervous system [6–8]. The use of transcranial magnetic stimulation (TMS) paired-pulse protocols to measure short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI) [9–11], and intracortical facilitation (ICF) has allowed for the evaluation of intracortical excitatory and inhibitory circuitry in RLS. Most of the previous studies on RLS using TMS have reported diminished inhibition (reduced SICI), with one study reporting increased ICF, thus suggesting an overall increased excitability and supporting hyperarousal. However, among prior studies on RLS using TMS, not all have had consistent results and these studies have been limited regarding RLS populations, study methods, and sample sizes. Additionally, most prior TMS studies that reported increased corticomotor excitability in RLS were primarily focused on the motor cortex of the hand [8,12–16]. There are only two studies that performed paired-pulse TMS [17,18] in the leg, which is the primary appendage affected by RLS. Most of the previous studies also did not consider the clinical aspects of RLS. Thus,

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putative mechanisms regarding cortical excitability, particularly for the leg motor cortex, underlying RLS, and the relationship of cortical excitability with clinical aspects of RLS, remain unclear.

This study, therefore, studied corticomotor excitability in the primary motor cortex (M1) of the hand and leg, along with examining the relationship to the clinical aspects of RLS and sleep parameters. Participants with RLS were compared to age-matched healthy good sleeper control participants who did not have significant periodic limb movements during sleep (PLMS) or a family history of RLS. The paired-pulse TMS measures SICI and LICI (extending on previous work) [9–11], were evaluated. The study also evaluated ICF, which is believed to predominately reflect glutamatergic-mediated excitability along with GABAergic processes [19]. The study was designed to test the hypothesis of basic glutamate-hyperarousal process producing both disrupted sleep (increased wake time) and corticomotor excitability (as demonstrated by TMS).

2. Methods

2.1. Participants

This study was approved by the Johns Hopkins Medicine Institutional Review Board, and participants provided written consent and were compensated. Thirty-five participants (20 F; mean age: 59.23 ± 1.66 years; range: 42–78 years) affected by primary RLS (off medications) and 31 age-matched controls (19 F; mean age: 57.90 ± 1.50 years; range: 43–79 years) were included in the study. Both right- and left-handed participants were included, but all participants had strong hand dominance, and none were ambidextrous (using the Edinburgh Handedness Inventory) [20]. All participants completed the Pittsburgh Sleep Quality Index (PSQI) [21] to assess sleep quality. Moreover, control participants demonstrated good sleep quality (PSQI < 5) [12]. Participants were not diagnosed with any sleep disorder other than RLS, any neurological disorder, nor with any major medical or psychiatric disorder (eg, congestive heart failure; stroke; seizure disorder; and history of psychotic disorders, dementia, or substance abuse). Menopausal status, menstrual cycle phase, and current use of hormone therapy were recorded and were balanced for women between groups as estradiol and the follicular phase of the menstrual cycle have been shown to affect glutamatergic [21,22], GABAergic activity [23,24], and cortical excitability [25]. Participants were not permitted to use alcohol, caffeine, or tobacco at any time during the study. None of the participants was on opioids, sedative hypnotics, antipsychotics, antidepressants, β-blockers, stimulants, mood stabilizers, or medications for thyroid/diabetes.

All participants with RLS fulfilled the criteria for a diagnosis of primary RLS through the validated Hopkins Telephone Diagnostic Interview [26] conducted by the principal investigator (RPA). This diagnosis was then reconfirmed by a board-certified sleep neurologist during the medical history and neurological examination (CJE or RMES) on admission day of the study. Participants with RLS passed a rigorous screening process, which included a tapering and discontinuation of any RLS medications (eg, dopamine agonists, dopaminergic agents, benzodiazepines, opiates, anticonvulsants, alpha-2 agonists, therapeutic cannabis, iron supplements, and/or melatonin) with 10 days off all RLS medications before admission to the Clinical Research Unit. History of augmentation was recorded for each participants with RLS [27]. Augmentation was identified from the clinical information collected at the time of the initial screening before any medication adjustment for this study. The identification followed recommended guidelines [28] (adjusted for the retrospective nature of the clinical information). Augmentation identification required that the RLS symptoms, compared to pretreatment, started at least 2 h earlier in the day or occurred with two or more of the following: spread to other body parts, marked decrease in duration of benefit from treatment, faster onset of symptoms when resting, increased RLS severity with increased treatment dose or increased severity of periodic limb movement (PLM) during resting, provided the change in symptoms could not be explained by change in patient status. Augmentation was identified without knowledge of any of biological measures that were performed in this study. While off medication, participants were monitored at home for periodic leg movements using Physical Activity Monitor–Restless Legs (PAM-RL) ambulatory leg monitors and software (Phillips-Respironics, Bend, Oregon) and were included in the study only if they averaged ≥15 PLMS per hour for 10 days. At the end of home-monitoring, enrolled RLS participants who scored <15 PLMS per hour (while off-medication; ie, post-holiday) on the International RLS Study Group severity scale (IRLS) [29] were excluded. Control participants went through much of screening processes same as those of the participants with RLS with some minor modifications (see below). All control participants had ≤10 PLMS per hour using PAM-RL leg activity monitors averaged for one week of monitoring.

3. Study design

3.1. Day 1 and day 2: sleep studies

Study participants were admitted to the Clinical Research Unit, an inpatient research unit that includes the Center in Sleep Research and Education (CISRE), and they completed the study in the next three days (Fig. 1). Participants had height, weight, and vitals recorded, and premenopausal female participants completed a urine pregnancy test to rule out possible pregnancy cases. All participants underwent for two nights inpatient sleep monitoring that consisted of full PSG at CISRE. Bed times were adjusted to match the participant's usual bedtime, including making adjustments for participants traveling from outside the Eastern Time Zone. Participants were excluded if apnea/hypopnea indices were >15 events per hour on the first night of the PSG studies, derived according to the American Academy of Sleep Medicine Criteria [30]. Control participants were excluded if they demonstrated a PLMS index of >15 events per hour on either of the two PSG studies.

3.2. Day 3: MRI

On Day 3, participants completed a brain MRI approximately 3 h after waking. MRI data were obtained on a 7-T scanner (Achieva; Philips Healthcare, Best, The Netherlands), using a 32-channel head coil and a head-only transmit coil (Nova Medical, Wilmington, MA). T1-weighted images were acquired using the MPRAGE sequence with (1 mm) isotropic resolution (TE/TR: 3.7/8 ms). A 2.5 cm × 2.5 cm × 2.5-cm voxel was positioned to include the motor hand knob [31], within the primary motor cortex (contralateral to the dominant hand) on the precentral gyrus, and placed to minimize inclusion of postcentral tissue that was used for the TMS session [32].

3.3. Day 3: transcranial magnetic stimulation (TMS)

3.3.1. Setup

TMS was performed on all participants between 10:00 and 12:00 in a quiet TMS laboratory setting following the MRI (Fig. 1). Participants were instructed to stay awake with eyes open for the TMS measures and were monitored visually by a study member. Participants recorded their level of sleepiness based on the single-item Stanford Sleepiness Scale [33] before and after TMS. Surface

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