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Original Article

Functional connectivity alternation of the thalamus in restless legs syndrome patients during the asymptomatic period: a resting-state connectivity study using functional magnetic resonance imaging

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ABSTRACT

Background: Restless legs syndrome (RLS) is a primary sensory disorder with a secondary motor component (e.g., urge to move), and the thalamus is known to play a central role in RLS. The purpose of our study was to explore the intrinsic changes in the thalamocortical circuit in RLS patients using a resting-state functional magnetic resonance imaging (fMRI) paradigm.
Methods: Resting-state fMRIs were obtained in the morning from 25 idiopathic RLS patients who were not using RLS medications and 25 controls. Resting-state connectivity was analyzed by a seed-based method using Analysis of Functional NeuroImages (AFNI) software with the bilateral thalami (ventroposterolateral nucleus [VPLN]). The connectivity characteristics of RLS patients were compared to those of the controls.
Results: We found that RLS patients showed reduced thalamic connectivity with the right parahippocampal gyrus, right precuneus, right precentral gyrus, and bilateral lingual gyri; however, the right superior temporal gyrus, bilateral middle temporal gyrus, and right medial frontal gyrus showed enhanced connectivity with the thalamus. RLS severity was negatively correlated with connectivity between the thalamus and right parahippocampal gyrus ($r = -0.414$; $P = .040$).
Conclusions: Our results suggest that the characteristics of the connectivity changes may reflect the pathways involved in producing RLS symptoms and indicate that RLS patients may have deficits in controlling and managing sensory information, which supports the act of viewing RLS as a disorder disrupting somatosensory processing.

1. Introduction

RLS is a primary sensory disorder characterized by an uncomfortable often hard to describe sensation in the legs intimately associated with an irresistible need or urge to move the legs (akathisia) [1]. Although much is known about the pathophysiology of this disease (e.g., brain iron insufficiency), substantially less is known about its neuroanatomic basis [2]. However, there are several studies in RLS populations that have implicated a role for the thalamus in this disease. A functional magnetic resonance imaging (fMRI) study showed that the akathisia experienced by RLS patients was associated with thalamic activation [3]. A voxel-based morphometry (VBM) study detected a bilateral gray matter increase in the medial and posterior portion of the thalamus [4]. A positron emission tomography study using [^{11}C] FLB 457 to investigate extrastriatal dopaminergic regions reported a higher binding potential in RLS patients at the level of the anterior cingulate cortex and of the medial and posterior subregions of the thalamus [5]. Using a proton magnetic resonance spectroscopy study, metabolic changes in the medial thalamus have been reported in RLS patients [6,7]. RLS symptoms also have been reported to develop after an insult to the ventrolateral thalamic nucleus [8].

As the thalamus is a crucial and central mediator of sensory input and perception with interactive connections to cortical and basal ganglia regions that mediate motivation, emotional drive,

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sleep-arousal and planning [9,10], it is reasonable to consider that alterations in thalamic function or its connections may be an important part of the anatomical basis for this disease. The resting-state fMRI paradigm, which reflects spontaneous neuronal activity [11], could provide insight into the intrinsic functional architecture of the thalamic connectivity in RLS. Making this assessment during the asymptomatic period allows us to determine the presence of altered systems connectivity, which may underlie this disease, but exclude any contamination of this system's analysis by the actual presence of the sensory symptoms (i.e., akathisia). Although RLS symptoms predominately present at night, there is support from several studies that sensory elements of RLS are compromised over the 24-h period. Patients with RLS who are placed at continuous rest over a 24-h period under a constant-routine paradigm will express symptoms throughout the 24-h period, but the degree of symptoms severity is markedly affected by circadian factors [12]. In addition, studies of pain perception have shown that RLS patients still show a significant reduction in their pain threshold even during the asymptomatic period [13]. The implications are that there may be a fixed or permanent alteration in sensory pathways, which underlies this disease and may form the basis for the development of the actual symptoms. This alteration should then be present even when not activated by factors producing the symptoms.

We hypothesized that an underlying component of the disease is an altered connectivity regarding the sensory pathways, which involve changes in the thalamic connectivity that would be evident during the asymptomatic period, and reflect a change in thalamocortical connectivity during resting-state conditions. To test this hypothesis, we used a resting-state fMRI paradigm, which reflects spontaneous neuronal activity, and could provide insight into the intrinsic functional architecture of the thalamic connectivity in RLS.

2. Methods

2.1. Study participants

The study was approved by the institutional ethics committee of the regional hospital. Informed consent was obtained from all participants. We enrolled 25 participants ages 18 years or older who were diagnosed as primary RLS and visited a sleep clinic in a University hospital and 25 age- and gender-matched healthy control participants who had no previous sleep problems in our study. A certified Korean neurologist, an expert in RLS, screened the participants using the diagnostic standards set by the National Institutes of Health RLS workshop [1]. All participants filled out the validated Korean version of the John Hopkins telephone diagnostic questionnaire [14,15] and confirmed their answers through face-to-face interviews and examinations to exclude any mimics of the disease. Patients with secondary RLS due to iron-deficiency anemia, pregnancy, chronic renal disease, peripheral neuropathy, myelopathy, and medication-induced RLS also were excluded. However, participants with only peripheral iron deficiency without definite cause were included. Participants with other comorbid sleep disorders, such as obstructive sleep apnea, parasomnia, and narcolepsy, were excluded through sleep questionnaires and polysomnography if needed.

Our primary measure of RLS disease burden was the validated Korean version of the International RLS Severity scale (K-IRLS) [16,17]. Because one of the primary consequences of RLS is sleep disruption, the Korean version of the Pittsburgh Sleep Quality Index and the Insomnia Severity Index (ISI) were used as secondary measure of RLS disease burden [18,19]. None of the RLS participants were taking any RLS medications and all had moderate to severe RLS symptoms. The control participants had no remarkable neurologic history or sleep disorders and answered no on the first two questions of the RLS diagnostic questionnaire [15,20]. The control participants also completed the Korean version of the Pittsburgh Sleep Quality Index and the ISI.

2.2. fMRI acquisition and analysis methods

The fMRI images were obtained in morning between 06:00 am and 09:00 am. The magnetic resonance imaging (MRI) scans were acquired using a 3 T MRI Signa Excite scanner (GE Healthcare, Milwaukee, WI, USA) with an 8-channel high-resolution brain coil. For each participant, an anatomic image series was obtained using a 3-dimensional spoiled gradient-echo sequence (TR = 6 s, TE = 2.2 s, flip angle = 20°, field of view = 240 mm, 256 × 256 matrix, 152 axial slices, and slice thickness = 2-mm thick). The functional images were collected using a gradient echo planar imaging sequence (TR = 2 s, TE = 17.6 s, flip angle = 90°, field of view = 240 mm, 64 × 64 matrix with 4-mm spatial resolution, 30

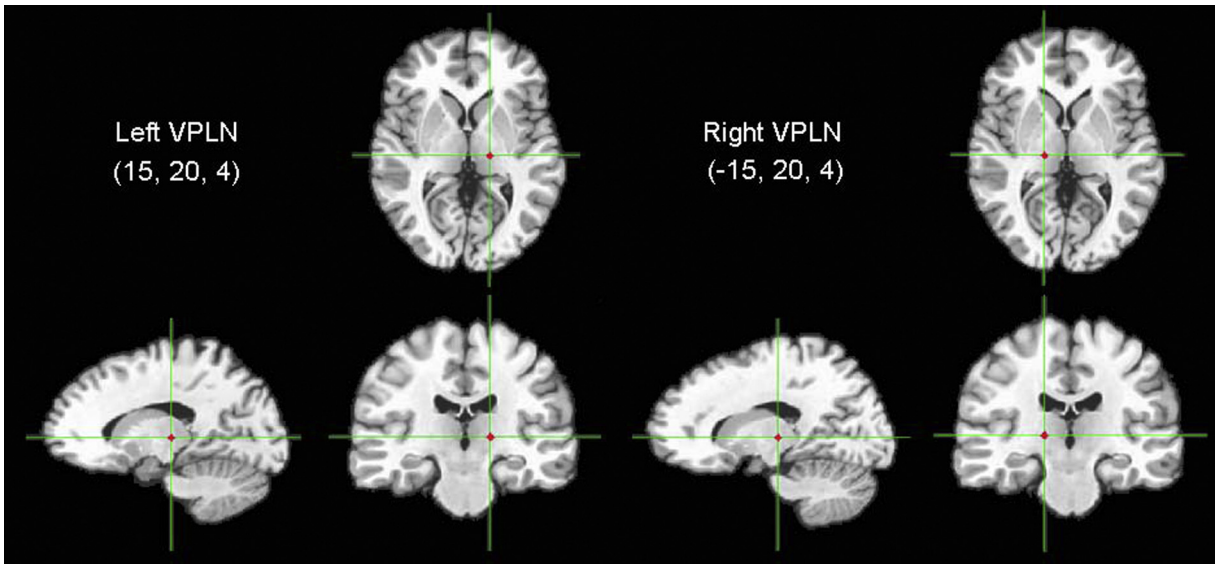

Fig. 1. The seed regions of interest were marked as 2-mm spheres in the left and right ventroposterolateral nuclei in the thalamus.