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Alterations of Functional Connectivity in Patients With Restless Legs Syndrome

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Restless legs syndrome (RLS) is a common neurological illness marked by a strong desire to move one's legs, usually in association with uncomfortable sensations. Recent studies have investigated brain networks and connectivity in RLS. The advent of network analysis has greatly improved our understanding of the brain and various neurological disorders. A few studies have investigated alterations in functional connectivity in patients with RLS. This article reviews functional connectivity studies of patients with RLS, which have identified significant alterations relative to healthy controls in several brain networks including thalamic, salience, default-mode, and small-world networks. In addition, network changes related to RLS treatment have been found, including to repetitive transcranial magnetic stimulation, transcutaneous spinal cord direct-current stimulation, and dopaminergic drugs. These findings suggest that the underlying pathogenesis of RLS includes alterations in the functional connectivity in the brain and that RLS is a network disorder.

Keywords restless legs syndrome; brain; magnetic resonance imaging.

INTRODUCTION

Restless legs syndrome (RLS) is a common neurological illness marked by a strong desire to move one's legs, usually in association with unpleasant sensations.[1,2] The reported prevalence of RLS ranges between 7% and 10% in the general adult population, and is more common in females than in males, with the prevalence increasing with age.[2-5]

Recent studies have increasingly focused on brain networks and connectivity. The advent of network analysis has greatly improved our understanding of the brain and various neurological disorders. Brain network analysis has been utilized in research to elucidate the physiological mechanisms underlying disease, as well as in clinical applications, where white-matter pathways may serve as a therapeutic target or represent regions that must be conserved during therapy.[6] Network analysis techniques can broadly probe structural and functional connectivity (Fig. 1). While structural connectivity is often used to investigate monosynaptic connections, functional connectivity can be used to identify polysynaptic connections by identifying areas exhibiting synchronized activity.[6] Furthermore, various methods can be used to investigate functional connectivity, including resting-state functional magnetic resonance imaging (rs-fMRI), EEG, magnetic encephalography, arterial spin labeling, and position-emission tomography.[7-9] rs-fMRI has been widely used in research, which reflects the coherence between temporal fluctuations in the blood-oxygen-level-dependent signals across brain regions.[7-9]

A few studies have examined the functional connectivity changes in patients with RLS (Table 1), and most of them have employed rs-fMRI. This article reviews the functional con-

Fig. 1. Methods of brain connectivity analysis.

nectivity studies of patients with RLS with the aim of obtaining a better understanding of the pathophysiology of RLS.

FUNCTIONAL CONNECTIVITY IN PATIENTS WITH IDIOPATHIC RLS

Thalamic network

Ku et al.[10] performed the first examination of functional connectivity in patients with RLS, in 2014. They enrolled 25 patients with RLS and 25 healthy controls who had undergone rs-fMRI. The functional connectivity of the bilateral thalami was investigated using a seed-based technique, since the thalamus plays a critical role in sensory input and perception.[11] They discovered that patients with RLS exhibited decreased thalamic connectivity to the right parahippocampal gyrus, right precuneus, right precentral gyrus, and bilateral lingual gyri, but increased connectivity to the right superior temporal gyrus, bilateral middle temporal gyri, and the right medial frontal gyrus. Additionally, the severity of RLS as measured using the International RLS Severity Scale (IRLS)[12] was negatively correlated with the connection between the thalamus and the right parahippocampal gyrus. Those findings indicated that RLS is a disorder that disrupts somatosensory processing,[10] and this was subsequently validated in a follow-up study published in 2020.[13] That study applied rs-fMRI to 32 patients with RLS and 16 healthy controls, and used a seed-based technique utilizing the bilateral ventral and posterolateral thalamic nuclei to assess functional connectivity changes in patients with RLS. Decreased functional connectivity changes were observed in the bilateral lingual gyri. However, the functional connectivity changes in the right middle temporal gyrus were greater in patients with RLS than in healthy controls. The results of these two studies suggest that the thalamic network is involved in the pathophysiology of RLS.[13]

Salience network

The salience network is important for recognizing and integrating emotional and sensory cues.[14] Because the primary complaint of patients with RLS is sensory symptoms, we may conclude that the salience network influences and recruits other brain networks, including those involved in sensory information processing.[14] This means that the salience network may be altered in patients with RLS.

Ku et al.[15] used rs-fMRI to investigate the functional connectivity between the salience network and other brain regions in patients with RLS. rs-fMRI was performed in 30 patients with RLS and 30 healthy controls during the asymptomatic phase of RLS. Those authors discovered a decrease in the right cerebellum's salience network and an increase in the bilateral orbitofrontal and right postcentral gyri salience networks. These findings show that salient stimuli may be identified erroneously in patients with RLS.

Alterations of the salience network were additionally confirmed by a recent rs-fMRI study conducted in Europe with a large sample of 82 patients with RLS and 82 healthy controls.[16] The connectivity of 12 resting-state networks, including the salience network, was investigated using the independent-component analysis method. Connectivity within the salience network and the executive and cerebellar networks was found to be significantly higher in the patients with RLS than in the healthy controls. These studies have demonstrated that the salience network is abnormal in patients with RLS.

Default-mode network

The default-mode network (DMN) is a network of brain regions connected to the posterior cingulate cortex that are active when an individual is not focused on the external environment, thereby indicating the cortical state of the brain during rest or when there is little external stimulation.[17]

The first study examining alterations in the DMN of patients with RLS was published in 2016,[18] in which rs-fMRI was used to compare the DMN between 16 patients with RLS and 16 healthy controls when they were in an asymptomatic resting state. That study found that patients with RLS had decreased DMN connectivity in the left posterior cingulate cortex, right orbitofrontal gyrus, left precuneus, right subcallosal gyrus, right superior parietal lobule, right supplementary motor area, and left thalamus. Patients with RLS may experience DMN disruptions that induce symptoms. Additionally, an increase in the thalamic circuit may act to suppress inner sensory input and may be associated with compensatory modi-

Table 1. Studies that have applied functional connectivity analysis to patients with RLS

Methodology	Nationality of the patients	No. of patients with RLS	Modality	Finding
Thalamic network				
Functional connectivity alternation of the thalamus in RLS during the asymptomatic period in the resting state using fMRI[10]	South Korean	25	rs-fMRI	Decreased thalamic connectivity to several gyri
Resting-state connectivity and the effects of treatment in RLS[13]	South Korean	32	rs-fMRI	Changes in thalamic connectivity to the lingual gyri and middle temporal gyrus
Salience network				
Alterations in salience network functional connectivity in RLS[15]	South Korean	30	rs-fMRI	Altered salience network during asymptomatic periods
Case–control investigation of functional connectivity and topology in RLS using rs-fMRI[16]	Austrian	82	rs-fMRI	Higher connectivity within salience network
DMN				
DMN disturbances in RLS/Willis-Ekbom disease[18]	South Korean	16	rs-fMRI	Disturbances of the DMN
Diurnal variation of the DMN in RLS[19]	South Korean	15	rs-fMRI	Diurnal disturbance of the DMN
Graph theoretical analysis				
Abnormal sleep delta rhythms and interregional phase synchrony investigated in RLS and their reversal by dopamine agonist treatment[23]	South Korean	12	EEG	Disrupted small-world network
Mapping the changed hubs and corresponding functional connectivity in idiopathic RLS[25]	Chinese	16	rs-fMRI	Functional connectivity changes in aberrant hubs
Case–control investigation of functional connectivity and topology in RLS using rs-fMRI[16]	Austrian	82	rs-fMRI	High clustering coefficient and local efficiency in motor regions
Other networks				
Association of patterns of increased intrinsic functional connectivity in RLS with attentional control of sensory inputs[26]	German	26	rs-fMRI	Increased connectivity in sensory, attentional, basal ganglia-thalamic, and cingulate networks
Mapping intrinsic functional brain changes and repetitive transcranial magnetic stimulation neuromodulation in idiopathic RLS using rs-fMRI[27]	Chinese	15	rs-fMRI	Small ALFF in sensorimotor and occipital regions
Investigating gray-matter density and functional connectivity of the pons in RLS[28]	Chinese	20	rs-fMRI	Changes in functional connectivity in the pons
Network changes related to RLS treatment				
Mapping intrinsic functional brain changes and repetitive transcranial magnetic stimulation neuromodulation in idiopathic RLS using rs-fMRI[27]	Chinese	15	rs-fMRI	rTMS increased ALFF in several sensorimotor and visual regions
Altered cortical gray-matter volume and functional connectivity after transcutaneous spinal cord direct-current stimulation in idiopathic RLS[30]	Chinese	30	rs-fMRI	tsDCS changed responses in sensorimotor and visual processing cortices
Resting-state connectivity and the effects of treatment in RLS[13]	South Korean	32	rs-fMRI	Dopamine agonist treatment changed in thalamic connectivity

Table 1. Studies that have applied functional connectivity analysis to patients with RLS (continued)

Methodology	Nationality of the patients	No. of patients with RLS	Modality	Finding
Case-control investigation of functional connectivity and topology in RLS using rs-fMRI[16]	Austrian	82	rs-fMRI	Dopamine agonist treatment increased connectivity between thalamus and frontal regions
Abnormal sleep delta rhythms and interregional phase synchrony investigated in RLS and their reversal by dopamine agonist treatment[23]	South Korean	12	EEG	Dopamine agonist treatment normalized the small-world network
Secondary RLS				
Reduced regional activity and functional connectivity in the sensorimotor network investigated in PD patients with RLS[35]	Chinese	14	rs-fMRI	Reduced brain activity in precentral gyrus in PD with RLS
Altered brain functional connectome in migraine with and without RLS investigated using rs-fMRI[38]	Taiwanese	22	rs-fMRI	Difference in salience, default-mode, and memory retrieval networks between migraine patients with and without RLS

ALFF, amplitude of low-frequency fluctuations; DMN, default-mode network; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; PD, Parkinson's disease; RLS, restless legs syndrome; rs-fMRI, resting-state functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; tsDCS, transcutaneous direct-current stimulation of the spinal cord.

fications that alleviate RLS symptoms.

Another study examined diurnal changes of the DMN in patients with RLS.[19] To account for the circadian rhythm, patients with RLS and healthy controls underwent rs-fMRI twice: once in the morning and once in the evening. Additionally, the DMN connections in patients with RLS and controls were evaluated. The theoretical foundation of that study was RLS symptoms varying throughout the day, with symptoms being most severe at night and least severe in the morning.[20] The results revealed substantial changes in DMN connections in both patients with RLS and controls in the morning and evening, as well as a constant increase in connectivity in the parietal lobule in the morning and evening. In contrast, the connectivity in the thalamus increased in the morning and decreased in the evening. This indicates that the onset of RLS symptoms is due to a reduced control mechanism represented by the dynamic diurnal system of RLS, which is related to the thalamic role of "resting keeper."[19] Furthermore, DMN activity varies significantly between healthy controls and individuals with RLS, and there are diurnal oscillations.

Graph theoretical analysis

The human brain is one of the most complicated networks known. The graph theory framework is a mathematical tool for simulating pairwise communications between the nodes of a network, and is therefore useful for understanding and modeling the brain.[21] Graph theory has revealed that the human brain network has the characteristics of a small-world network that is optimal for interregional information transfer and is highly efficient.[22] However, graph theory has so far been used in only three investigations of RLS.

The first functional connectivity study using graph theory was performed in South Korea and published in 2017, and is still the only study to use EEG to evaluate functional connectivity in patients with RLS.[23] That study enrolled 12 patients with RLS and 16 healthy controls, with nightly polysomnography (PSG) with 19-channel EEG recording performed on the RLS patients. Interregional phase synchronization was determined by calculating phase coherence in 30-s epochs, and network dimensions were determined using graph theoretical analysis. The results indicated that patients with RLS experienced disruption of the small-world network during deep sleep, which was attributed to decreases in the local clustering coefficients.

In the brain, highly connected and central nodes, called "hub nodes," play a critical role in the global topology of the whole-brain network.[24] Liu et al.[25] used rs-fMRI and graph theory to determine if the presence of hubs differed between patients with RLS and healthy controls. They analyzed the functional connectivity patterns of aberrant hubs in 16 patients with RLS and 26 healthy controls, and found that the functional connectivity was weaker in patients with RLS than in the healthy controls in the cuneus, fusiform gyrus, paracentral lobe, and precuneus, but stronger in the superior frontal gyrus and thalamus.[25]

The European study described above that identified changes in the salience network also used graph theory to conduct a network analysis of patients with RLS.[16] Compared with healthy controls, patients with RLS had considerably higher clustering coefficients and local efficiencies in the motor and frontal regions, and significantly lower clustering coefficients in the central sulcus, central opercular cortex, and temporal, parieto-occipital, cuneus, and occipital regions. The authors hypothesized that changes in the motor areas could be associated with the need of patients with RLS to move.[16] These investigations all support the presence of marked changes in both the global and local functional brain architecture in patients with RLS.

Other networks

A study published in 2016 used rs-fMRI to examine changes in whole-brain functional connectivity in patients with RLS.[26] The motor/sensorimotor, sensory thalamic, ventral and dorsal attention, basal ganglia-thalamic, cingulate, and brainstem networks were compared between 26 patients with RLS and 26 healthy controls. That study found that functional connectivity was increased in patients with RLS in the limbic, dorsal, and ventral attention networks and the basal ganglia-thalamic networks, but not in the motor/sensorimotor or brainstem. It was particularly interesting that, unlike the earlier investigation by Liu et al.,[27] the 2016 study did not identify any changes in functional connectivity in the sensory and motor networks. The authors concluded that the pathophysiology causing RLS extends beyond the sensorimotor and brainstem systems and may be associated with impaired attentional regulation of sensory inputs.[26]

Another study employed rs-fMRI to assess changes in functional connectivity in 20 patients with RLS and 18 healthy controls.[28] That study found significant decreases in the functional connectivity between the midbrain and the right middle occipital gyrus, between the pons and the right orbital part of the superior frontal gyrus, and between the pons and the right parahippocampus, and a significant increase between the pons and the right supplementary motor area. These data show that RLS may be related to brainstem anomalies, particularly in the pons.[28]

Network changes related to RLS treatment

The first study of network changes associated with RLS treatments examined the impact of repetitive transcranial magnetic stimulation (rTMS) on brain connectivity in patients with RLS.[27] Those authors used rs-fMRI to compare the amplitudes of low-frequency fluctuations (ALFFs) between 15 patients with RLS and 14 healthy controls. The ALFF is calculated as the square root of the power spectral density between 0.01 and 0.08 Hz, which corresponds to the spontaneous neural activity in the brain.[29] Those authors discovered that the ALFF in patients with RLS was lower in sensorimotor and visual processing regions and higher in the insula, parahippocampal and hippocampal gyri, left posterior parietal areas, and brainstem, indicating that patients with RLS and healthy controls exhibit distinct types of spontaneous brain activity. Seven of the 15 patients with RLS underwent high-frequency rTMS directed at the leg area of the primary motor cortex, which increased the ALFF in sensorimotor and visual processing regions, indicating improved RLS symptoms as measured by the IRLS following rTMS. These findings suggest a mechanism of action for rTMS treatment in patients with RLS.[27]

Another study employed transcutaneous direct-current stimulation of the spinal cord (tsDCS).[30] Numerous studies have found that disrupting the descending inhibitory pathway of the central nervous system contributes to the pathophysiology of RLS, and that tsDCS can alter the activity of the spinal cord conduction tract and loop, implying that tsDCS could play a role in RLS therapies.[31,32] In the study of Wang et al.,[30] all patients with RLS were randomly assigned to either anodal treatment or a sham treatment, and functional connectivity alterations were assessed using rs-fMRI. Significant changes were observed in the anodal therapy group but not in the sham-treatment group. The functional connectivity increased significantly between the bilateral cuneus and left primary visual cortex and between the right cuneus and right lingual gyrus following tsDCS, while it decreased significantly between the left ventral postcentral gyrus and supplementary motor area.[30] The authors concluded that tsDCS may be used to modulate functional connectivity in the sensorimotor and visual processing cortices so as to alleviate RLS symptoms.

Three recent investigations used rs-fMRI to assess functional connectivity alterations following dopaminergic medication therapy.[13,16] Lee et al.[13] investigated functional connectivity differences in 16 patients with RLS after the administration of dopamine agonists, and discovered increased thalamocortical connectivity in the left uvula, right tuber, left anterior insula, and right declive in drug-treated RLS patients compared with drug-naive RLS patients. That study demonstrated the considerable effects that dopaminergic drugs can exert on brain networks. Thus, dopaminergic medication therapy altered brain regions that are linked with symptom management but not with RLS networks. Tuovinen et al.[16] investigated functional connectivity in RLS patients with and without dopaminergic treatment using rs-fMRI. They found greater connectivity between the right orbital sulcus and right thalamus in patients receiving dopaminergic medication than in those who had not undergone therapy. Choi et al.[23] combined PSG and EEG-based graph theory to examine functional connectivity in individuals with RLS before and after dopamine agonist treatment. They found disturbances of the small-world network, which were reversible with a dopamine agonist. All of these findings demonstrate that RLS treatment can influence functional connectivity in patients with RLS. Future studies of RLS should investigate whether the changes in functional connectivity following RLS therapy are reversible.[33]

FUNCTIONAL CONNECTIVITY IN PATIENTS WITH SECONDARY RLS

Only two reported studies have performed functional connectivity analyses of patients with secondary RLS. The probability of developing RLS is roughly two- to threefold higher in Parkinson's disease (PD) patients than in the general population,[34] and the reported prevalence of RLS in patients with PD ranges between 3% and 50%.[34] Li et al.[35] used rs-fMRI and regional homogeneity metrics to examine the functional connectivity differences between 14 patients with PD and RLS and 20 patients with PD but not RLS in 2019. Brain activity in the right precentral gyrus was lower in the PD patients with RLS, and it decreased as the severity of RLS increased. Additionally, in the seed-based approach, the functional connectivity between the right precentral gyrus and the left postcentral/precentral gyri differed between the PD patients with and without RLS. These findings suggest that functional anomalies in the sensorimotor network interfere with the pain pathway, resulting in RLS symptoms in patients with PD.[35]

The second study that performed functional connectivity analyses of patients with secondary RLS involved patients with migraine. RLS is a frequent comorbidity in patients with migraine, and the frequency of RLS is significantly higher in patients with migraine than in the general population with an odds ratio of 1.20.[36] Approximately 16% of patients with migraine had RLS.[37] Yang et al.[38] used rs-fMRI and network-wise

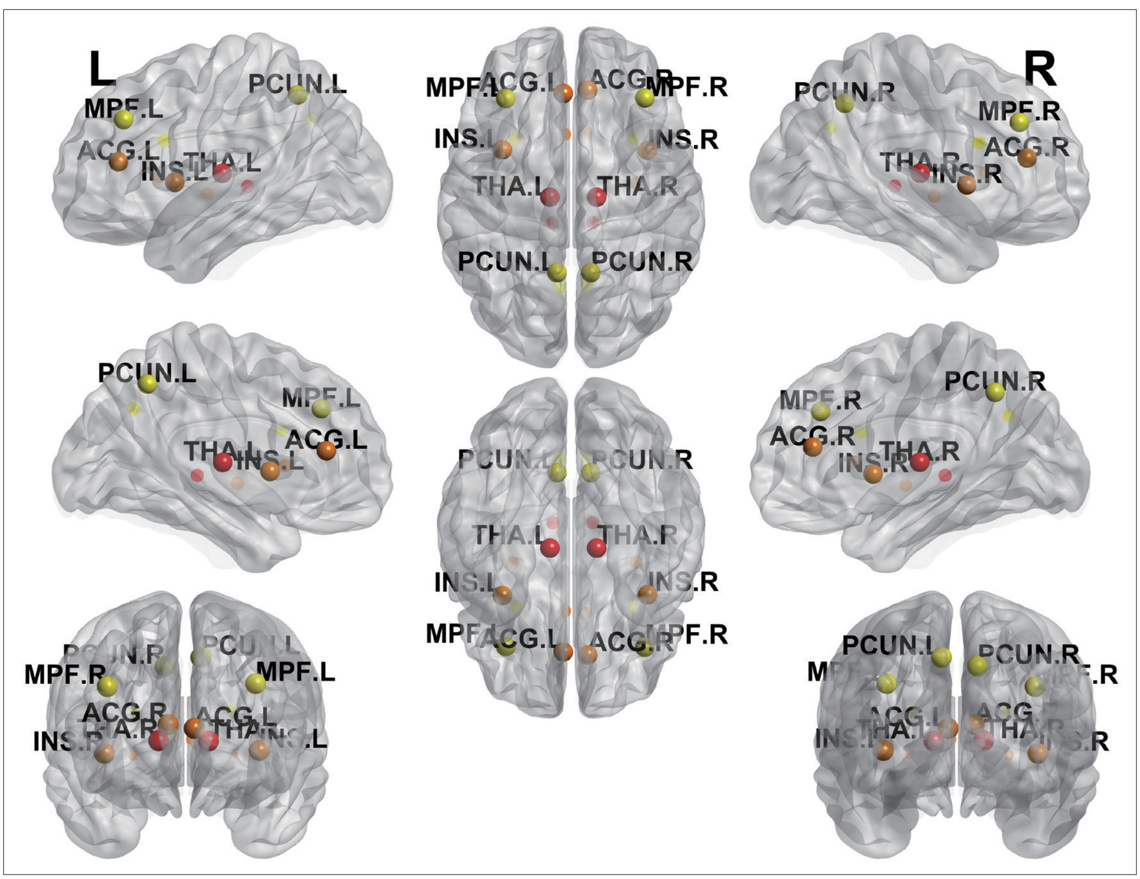

Fig. 2. Hub nodes of the networks showing significant differences between patients with restless legs syndrome and healthy controls. Red, orange, and yellow circles indicate the hub nodes of the thalamic network consisting of the thalamus (THA), of the salience network consisting of the anterior insula (INS) and the dorsal anterior cingulate cortex (ACG), and of the default-mode network consisting of the medial prefrontal cortex (MPF) and precuneus (PCUN), respectively. L, left; R, right.

analysis of functional connectivity to compare 22 patients with migraine and RLS with 22 patients with migraine but not RLS. They revealed significant differences between patients with migraine with and without RLS in the functional connectivity of the salience network, of the DMN to subcortical and frontoparietal networks, of the auditory network to the salience network, and of the memory retrieval network. Additionally, a negative correlation was found between the severity of RLS and the connection between the DMN and subcortical network. Those authors concluded that these functional intergroup differences could be explained by differences in the attentional nociceptive regulation of sensory inputs, which could also account for the clinical disparities observed between migraine patients with and without RLS. These two investigations demonstrate that functional connectivity in patients with PD or migraine differs according to the presence or absence of RLS.

The above-described previous studies of functional connectivity in RLS had several limitations. First, many of these studies had a cross-sectional design, which would not reveal the causal relationship between alterations of functional connectivity and RLS symptoms. Future longitudinal studies are therefore needed. Second, most of the studies involved a single center with a small sample. Multicenter researches with large samples are therefore also needed to confirm the findings. Third, all but one of the studies used rs-fMRI to investigate alterations of functional connectivity in RLS. Although rs-fMRI is one of the most common methods used to investigate functional connectivity, it has low spatial resolution and is sensitive to noise that is unrelated to the neuronal functioning of the brain, such as that due to cardiac activity and respiration.[39] Other methods including magnetic encephalography, EEG, perfusion magnetic resonance imaging, and positron-emission tomography could be used to investigate alterations of functional connectivity in patients with RLS in the future.

CONCLUSION

Alterations in brain networks such as the thalamic, salience, default-mode, and small-world networks have been reported in patients with RLS (Fig. 2). Reduced brain iron levels and dopaminergic dysfunction trigger and influence several pathways and networks. In addition, RLS treatments including rTMS, tsDCS, and administration of dopaminergic drugs can induce changes in these networks. Alterations in functional connectivity represent the underlying pathogenesis of RLS, and suggest that RLS is a type of network disorder with different phenotypes.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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