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Alterations of the brain network in idiopathic rapid eye movement sleep behavior disorder: structural connectivity analysis

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Abstract

Purpose To evaluate and compare structural connectivity using graph theoretical analysis in patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) and healthy subjects.

Methods Ten consecutive patients with iRBD were recruited from a single tertiary hospital. All patients had normal brain magnetic resonance imaging results on visual inspection. They did not have any other neurological disorder. Control subjects were also enrolled. All subjects underwent three-dimensional volumetric T1-weighted imaging. Absolute structural volumes were calculated using FreeSurfer image analysis software. Structural volume and connectivity analyses were performed with Brain Analysis using Graph Theory.

Results Compared to healthy controls, patients with iRBD showed significant alterations in cortical and subcortical volumes, showing increased volumes of frontal cortex, thalamus, and caudate nucleus. In addition, patients with iRBD exhibited significantly different structural connectivity compared to healthy controls. In measures of global network, average degree, global efficiency, and local efficiency were decreased whereas characteristic path length was increased in iRBD patients. In measures of local network, there was significant hub reorganization in patients with iRBD. Betweenness centrality of caudate nucleus and frontal cortex was increased in patients with iRBD.

Conclusions This is the first study to report that structural volume and connectivity in patients with iRBD are significantly different from those in healthy controls. iRBD patients exhibited disrupted topological disorganization of the global brain network and hub reorganization. These alterations are implicated in the pathogenesis of iRBD. They might be potential biomarkers of iRBD.

Keywords REM sleep behavior disorder · Graph theory · Network · Magnetic resonance imaging

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is one of the disorders of parasomnia, which characterized by the loss of normal muscle atonia and increased motor activity during REM sleep. RBD occurs either as an idiopathic disease or in association with neurodegenerative disease(s), particularly alpha-synucleinopathies [1, 2]. Idiopathic RBD (iRBD) refers to the occurrence of RBD in the absence of any other neurological condition [1, 2]. iRBD continues to attract attention because it often precedes the onset of neurodegenerative disease [1, 2].

Few studies have examined structural changes of the brain in patients with iRBD. One study using voxel-based morphometry (VBM) has showed significant gray matter volume reduction in the cerebellum, pons, and parahippocampal gyrus in patients with iRBD [3]. Another study has reported increases in gray matter densities in both hippocampi of patients with iRBD [4]. In addition, one study investigating gray matter thickness has reported decreased cortical thickness in the frontal cortex, lingual gyrus, and fusiform gyrus of patients with iRBD [5]. Moreover, studies based on diffusion tensor

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imaging have demonstrated significant microstructural changes in the white matter of the brainstem, substantia nigra, olfactory region, temporal lobe, fornix, internal capsule, corona radiata, and the visual stream in patients with iRBD [4, 6]. All these studies suggest that loss of REM sleep atonia in RBD can be attributed to cortical and subcortical changes as well as brainstem dysfunction [7]. However, no studies have investigated structural connectivity of the brain network in patients with iRBD.

Graph theoretical analysis is a tool that takes a quantification brain connectivity and network [8, 9]. It can make a complex brain network into a simple model of the underlying brain connectivity, which is represented by nodes and edges using mathematical analysis. By reducing the complex brain network into a set of simple network measures that characterize specific topological properties of the brain network, it is able to connect investigations of individual connectivity of nodes and the global network as a whole. This approach has made considerable impacts on recent researches investigating the brain network and has enabled the discovery of small-world architectures of human brain. This small-world network is characterized by high levels of integration and segregation [8–10].

The objective of the present study was to evaluate alterations of structural volume and connectivity using graph theoretical analysis in patients with iRBD compared to healthy subjects.

Methods

Subjects

This study was conducted with the approval of the authors' Institutional Review Board. Ten consecutive patients with iRBD were recruited from a single tertiary hospital. All patients had a typical history of dream-enacting behaviors described by their family members. The diagnosis of RBD was made on the basis of polysomnographic evidence according to international diagnostic criteria for RBD which required either sustained elevation of chin electromyography activity during sleep stage R (> 50% of the 30 s epoch duration compared with minimum amplitude in non-sleep stage R) or excessive bursts of transient muscle activity in chin or limb electromyography during sleep stage R (at least one-half of all 3 s mini epochs on a 30 s page) [11]. All patients underwent brain magnetic resonance imaging (MRI) including three-dimensional (3D) T1-weighted imaging suitable for structural volume analysis and Seoul Neuropsychological Screening Battery to exclude the presence of cognitive decline. They exhibited no signs or symptoms of other neurological diseases or RBD secondary to medication. Fourteen age- and sex-matched healthy subjects without any significant neurological or psychiatric history were also enrolled for the control group. They had normal MRI on visual inspection.

Brain MRI data acquisition, processing, and analysis using FreeSurfer

We described the process of brain MRI data acquisition, processing, and analysis using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) on a 64-bit Linux CentOS in our previous study [12]. Briefly, all MRI scans were performed using a 3.0 Tesla MRI scanner. All subjects underwent conventional brain MRI protocols, including axial and coronal two-dimensional (2D) T2- and T1-weighted imaging. In addition, axial and coronal 2D fluid-attenuated inversion recovery images (FLAIR) were obtained to evaluate structural lesions. All of the subjects underwent sagittal-oriented 3D T1-weighted imaging suitable for structural volumetric analysis. Then, the processing stream of volumetric structural analysis using FreeSurfer automated imaging analysis suite was conducted. Brain structures were also segmented automatically based on T1-weighted images, and absolute structural volumes were calculated from them. Volumetric measures were then calculated using the following equation:

$$\text{Structural volumes}\ (\%) = (\text{absolute structural volumes}/\text{total intracranial volumes}) \times 100.$$

Structural volume and connectivity analysis using graph theory

Structural volume and connectivity analysis were performed with Brain Analysis using Graph Theory (BRAPH; http://braph.org) [13]. In this study, brain networks were built for each group as a collection of nodes representing brain regions connected by edges corresponding to connections between them. Nodes were defined based on cortical volumes from 60 cortical and 13 subcortical regions provided by FreeSurfer (Suppl. 1 and 2). Edges were calculated as partial correlation coefficients between every pair of brain regions while controlling for effects of age and sex. For each group, a structural weighted connectivity matrix was built. To detect differences in global network topology between groups, average degree, characteristic path length, mean clustering coefficient, global efficiency, local efficiency, and small-worldness index were calculated. The average degree is an average number of connections that link it to the rest of the network [8]. The path length refers to the number of edges that should be traversed to go from one node to another node. The characteristic path length represents the functional network integration of the brain as the average of the shortest paths of all nodes. [10]. The mean clustering coefficient is a measure of segregation. It defines the connection probability of the nearest

neighboring nodes. Thus, it is regarded as a measure of local connectedness within a network [10]. The efficiency is the inverse of the shortest path. The global efficiency defines the efficiency of the information transfer from one region to the whole network, which assesses the shortest path length between one node and all other nodes in the network. The local efficiency defines the efficiency of the information transfer from each region to the neighboring regions, and the local efficiency of the network is conventionally defined as the average of the local efficiencies of all nodes [8]. The small-worldness index is a proportion between the ratio of the network's mean clustering coefficient to that of a set of random networks with similar link weight distribution. It is the ratio of the network's characteristic path length to that of a set of random networks with similar link weight distribution [9]. To assess differences in local network topology between groups, the betweenness centrality was calculated. It identifies nodes located on the most traveled paths by measuring the number of shortest pathways in the network that passes through a given node [9].

Statistical analysis

Differences in structural volume between patients with iRBD and healthy controls were assessed using Student's t test. In addition, statistical differences in global and local network measures between patients with iRBD and healthy controls were assessed using nonparametric permutation tests with 1000 permutations.

In the randomization process, the cortical and subcortical volumes of the control and the patient groups were randomly assigned to groups A and B as the control and the patient groups, respectively, and this process was repeated 1000 times. Then, volumetric correlation matrices were generated from both groups, and the network parameters were calculated for each matrix. The differences in the network parameters between groups A and B were evaluated, and the permutation distribution was obtained by frequency analysis. On the permutation distribution analysis, the locations of the network parameters of the control and the patient groups were obtained, and statistical significance was acquired by the two-sided test. Ninety-five percent confidence intervals (CIs) of each distribution were used as critical values for a two-tailed test of null hypothesis at $p < 0.05$.

Results

Demographic characteristics of the study population

Of 10 patients with iRBD, 6 (60%) were males and 4 (40%) were females. Their mean age (± SD) was 67.0 ± 6.4 years. The control group consisted of 14 age- and sex-matched healthy subjects, of whom 8 (57.1%) were males and 6 (42.9%) were females. Their mean age was 67.2 ± 4.5 years. The mean age or sex ratio in healthy subjects was not statistically different from that in patients with iRBD ($p = 0.9241$, $p = 1.000$, respectively). Polysomnography revealed 308.9 ± 53.1 min of mean sleep time, 10.0 ± 6.3% of mean ratio of sleep stage R, 70.0 ± 8.9% of mean sleep efficiency, and 3.4 (0.0–4.9) of median apnea-hypopnea index.

Differences in structural volumes

There were significant alterations in cortical and subcortical volumes of patients with iRBD compared to healthy controls (Fig. 1, Suppl. 1). For cortical structures, volumes of the pars opercularis cortex in the left hemisphere and isthmus cingulate cortex in the right hemisphere were decreased (0.257% versus [vs.] 0.297%, $p = 0.047$; 0.139% vs. 0.153%, $p = 0.035$, respectively), whereas those of lateral orbitofrontal and rostral middle frontal cortex in the right hemisphere were increased in patients with iRBD compared to those in healthy controls (0.454% vs. 0.411%, $p = 0.036$; 0.972% vs. 0.905%, $p = 0.040$, respectively). For subcortical structures, volumes of the thalamus in the left hemisphere (0.533% vs. 0.461%; $p = 0.004$) and thalamus and caudate nucleus in the right hemisphere were increased in patients with iRBD compared to those in healthy controls (0.465% vs. 0.418%, $p = 0.021$; 0.239% vs. 0.199%, $p = 0.018$, respectively).

Differences in structural connectivity

For measures of global network, there were significant differences between patients with iRBD and healthy controls (Table 1). For patients with iRBD, average degree,

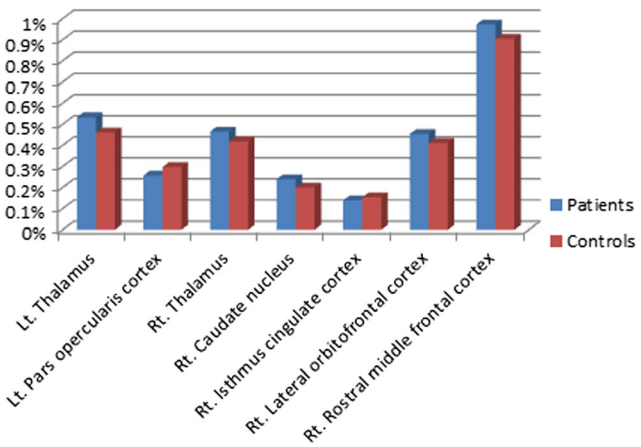

Fig. 1 Differences in structural volumes. Significant alterations in cortical and subcortical volumes in patients with idiopathic rapid eye movement sleep behavior disorder compared to healthy controls

Table 1 Differences in global structural connectivity in patients with idiopathic rapid eye movement sleep behavior disorder compared to healthy controls

Network measure	Patients	Controls	Difference	CI lower	CI upper	*p* value
Average degree	45.3699	69.6986	24.3288	− 13.9478	20.9965	0.041*
Characteristic path length	3.5472	2.1302	− 1.4171	− 1.0700	1.4640	0.029*
Global efficiency	0.3307	0.5269	0.1962	− 0.2168	0.1661	0.040*
Local efficiency	0.9370	2.3991	1.4622	− 1.6904	1.1607	0.032*
Mean clustering coefficient	0.2152	0.4716	0.2563	− 0.2553	0.2248	0.0610
Small-worldness index	0.9039	0.9500	0.0461	− 0.0352	0.0591	0.2830

*Statistically significant difference (i.e., $p < 0.05$)

CI 95% confidence interval

global efficiency, and local efficiency were decreased (45.369 vs. 69.698, $p = 0.041$; 0.330 vs. 0.526, $p = 0.040$; 0.937 vs. 2.399, $p = 0.032$, respectively) whereas the characteristic path length was increased compared to that in healthy controls (3.547 vs. 2.130; $p = 0.039$). However, mean clustering coefficient or small-worldness index in patients with iRBD was not significantly different from that in healthy controls. For measures of local network, there was significant hub reorganization in patients with iRBD compared to healthy controls (Fig. 2, Suppl. 2). The betweenness centralities of the left caudate nucleus, caudal middle frontal, lateral orbitofrontal and superior frontal cortex, and the right caudate, caudal middle frontal, pars triangularis, and rostral middle frontal cortex in patients with iRBD were increased (0.019 vs. 0.000, $p = 0.023$; 0.013 vs. 0.000, $p = 0.049$; 0.036 vs. 0.003, $p = 0.008$; 0.029 vs. 0.001, $p = 0.044$; 0.024 vs. 0.000, $p = 0.032$; 0.020 vs. 0.000, $p = 0.019$; 0.041 vs. 0.000, $p = 0.001$; 0.002 vs. 0.004, $p = 0.027$, respectively) whereas that of the pars orbitalis in the right hemisphere was decreased compared to healthy controls (0.000 vs. 0.036, $p = 0.002$).

Discussion

The main finding of the present study was that structural connectivity in patients with iRBD was significantly different from that in healthy controls. Patients with iRBD exhibited disrupted topological disorganization of the global brain network. Additionally, hub reorganization of the local brain network, particularly the caudate nucleus and the frontal cortex, had pivotal roles as a hub. Furthermore, our study confirmed results of previous reports describing alterations in structural volumes of patients with iRBD. These alterations of structural volume and connectivity might be implicated in the pathogenesis of iRBD. They might be potential biomarkers of iRBD.

The structural organization of the human brain has highly efficient and nonrandom, which is achieved through an orderly growth process with highly optimized efficiency. It is related to the balance of segregation and integration [14]. However, previous studies using graph theoretical analysis have reported the presence of topological disorganization of the brain network in patients with various neurological disorders, including epilepsy [12], dementia [15], and Parkinson's disease [16], resulting in decreased efficiency of the brain

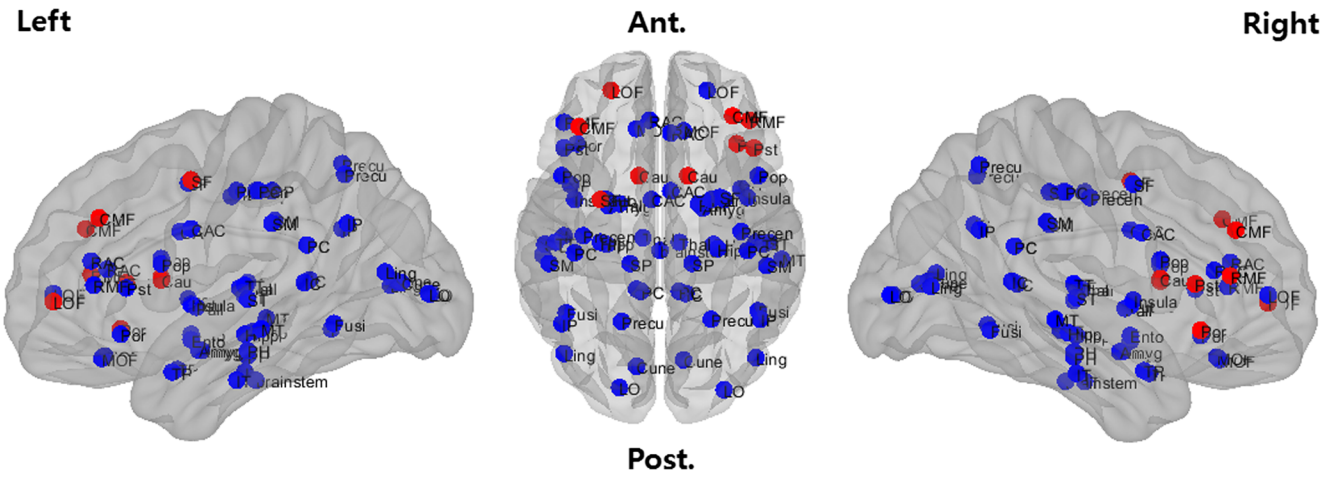

Fig. 2 Differences in local structural connectivity. Circles represent nodes of the brain. Red circles indicate regions of hub reorganization in patients with idiopathic rapid eye movement sleep behavior disorder compared to healthy controls. CAU: caudate nucleus; CMF: caudal middle frontal cortex; LOF: lateral orbitofrontal cortex; SF: superior frontal cortex; Por: pars orbitalis cortex; Pst: pars triangularis cortex; RMF: rostral middle frontal cortex

network compared to healthy subjects. We found that the average degree, global efficiency, and local efficiency were decreased whereas characteristic path length was increased in patients with iRBD compared to healthy subjects. All these changes can lead to decreased integration and segregation, resulting in low efficiency of the brain network in patients with iRBD, suggesting that iRBD is a network disease [8, 14].

Among hypotheses proposed to explain the pathophysiology of iRBD, alteration of a basal ganglia network has been suggested as a reason for the loss of REM atonia in iRBD [17–20]. Recently, Rolinski et al. have reported that widespread aberrant connectivity within the basal ganglia network, including caudate nucleus, is detectable using resting state functional MRI in patients with iRBD who do not manifest significant motor impairment [20]. Several single-photon emission-computed tomography (SPECT) studies have found reduced striatal dopaminergic innervation in patients with iRBD [19, 21, 22]. The loss of inhibitory nigrostriatal dopaminergic projections to the indirect pathway may result in a functional overactivity of the caudate nucleus and putamen with consequent increase in phasic discharges in the internal pallidum [23]. This activity, by excessively inhibiting the midbrain extrapyramidal area, could underlie the expression of excessive nocturnal movements in iRBD. Therefore, overactivity of the caudate nucleus could be a factor in the pathophysiology of iRBD by exacerbating alteration of brainstem network. Consistent with these previous reports, we found increased centrality measures of the caudate nucleus in patients with iRBD compared to healthy subjects, suggesting alteration of brain ganglia network in patients with iRBD, especially overactivity of the caudate nucleus. Furthermore, our finding demonstrated an increase in caudate nucleus volume in patients with iRBD compared to healthy controls. To the best of our knowledge and, in contrast to previous studies based on functional neuroimaging techniques, this is the first study to report changes of structural volume and connectivity in the basal ganglia, especially the caudate nucleus.

Another important finding was that volumes of lateral orbitofrontal, rostral middle frontal cortex, and thalamus were increased. Betweenness centralities of the caudal middle frontal, lateral orbitofrontal, superior frontal cortex, and rostral middle frontal cortex were also increased in patients with iRBD compared to healthy controls. Present findings are consistent with a previous report using 18F-fluorodeoxyglucose positron emission tomography in patients with iRBD [24], identifying an RBD-related metabolic network characterized by increased activity in the thalamus and medial frontal and sensorimotor areas. In addition, Sunwoo et al. [25] have evaluated resting-state electroencephalography functional connectivity to identify brain network changes in patients with iRBD. They found that iRBD patients exhibited decreased delta-band functional connectivity in frontal regions. They also revealed that altered connections had significant correlation with RBD questionnaire scores [25]. In accordance with these previous reports, results from the current study highlighted that aberrant networks mainly involved the connectivity of frontal regions. We speculate that these cortical activations of the frontal lobe might produce overactivity in the striatum, including the caudate nucleus, resulting in the expression of excessive nocturnal movement in individuals with iRBD.

Aberrant connectivity within the basal ganglia network has already been replicated in a previous study involving patients with Parkinson's disease [26]. Moreover, studies using dopamine transporter SPECT have reported that patients with iRBD demonstrate significantly reduced tracer uptake in the basal ganglia, both at baseline and at 3-year assessment when compared with healthy controls. These studies highlight nigro-putaminal de-afferentation as a marker of increasing severity of Parkinson's disease whereas nigro-caudate de-afferentation could be a hallmark of RBD, independent of a diagnosis of Parkinson's disease [21, 22]. This is consistent with the hypothesis that iRBD may represent the prodromal stage of Parkinson's disease, with an estimated period of 10 to 15 years of progressive neuronal loss before the onset of core motor symptoms [27]. Notably, a similar pattern of network alteration in the frontal lobe has already been reported in neurodegenerative diseases. In amnestic mild cognitive dysfunction, a lower level of delta-band phase synchronization has also been found in frontotemporal and frontoparietal connections [28]. Considering these findings, alteration of the brain network is a common pathophysiological mechanism for iRBD and neurodegenerative diseases, suggesting that patients with iRBD might have already entered an early stage of a neurodegenerative process not yet clinically apparent.

This study has several limitations. First, it had relatively small number of subjects. Therefore, our results require confirmation with larger cohorts. Nevertheless, the fact that a small number of samples has produced statistically significant results in structural connectivity analysis suggests that our results are meaningful. In addition, recruiting large numbers of iRBD patients with normal MRI features and cognitive function on visual inspection is difficult. Second, this was a cross-sectional study. Thus, we were not able to determine a causal relationship between alterations of structural volume and connectivity and the development of iRBD.

Conclusions

The present study was the first to identify that structural volume and connectivity in patients with iRBD were significantly different from those in healthy controls. Topological disorganization of the global brain network and hub reorganization were disrupted in patients with iRBD. These alterations are implicated in the pathogenesis of iRBD. They might be potential biomarkers of iRBD.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal consent was not required for a study of this type.

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