Original Article | Neuroimaging and Head & Neck

eISSN 2005-8330
https://doi.org/10.3348/kjr.2022.0712
Korean J Radiol 2023;24(3):247-258

Korean Journal of Radiology
KJR

Neuroanatomical Localization of Rapid Eye Movement Sleep Behavior Disorder in Human Brain Using Lesion Network Mapping

Taoyang Yuan[1], Zhentao Zuo[2], Jianguo Xu[1]

[1]Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China
[2]State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Objective: To localize the neuroanatomical substrate of rapid eye movement sleep behavior disorder (RBD) and to investigate the neuroanatomical locational relationship between RBD and α-synucleinopathy neurodegenerative diseases.
Materials and Methods: Using a systematic PubMed search, we identified 19 patients with lesions in different brain regions that caused RBD. First, lesion network mapping was applied to confirm whether the lesion locations causing RBD corresponded to a common brain network. Second, the literature-based RBD lesion network map was validated using neuroimaging findings and locations of brain pathologies at post-mortem in patients with idiopathic RBD (iRBD) who were identified by independent systematic literature search using PubMed. Finally, we assessed the locational relationship between the sites of pathological alterations at the preclinical stage in α-synucleinopathy neurodegenerative diseases and the brain network for RBD.
Results: The lesion network mapping showed lesions causing RBD to be localized to a common brain network defined by connectivity to the pons (including the locus coeruleus, dorsal raphe nucleus, central superior nucleus, and ventrolateral periaqueductal gray), regardless of the lesion location. The positive regions in the pons were replicated by the neuroimaging findings in an independent group of patients with iRBD and it coincided with the reported pathological alterations at post-mortem in patients with iRBD. Furthermore, all brain pathological sites at preclinical stages (Braak stages 1–2) in Parkinson's disease (PD) and at brainstem Lewy body disease in dementia with Lewy bodies (DLB) were involved in the brain network identified for RBD.
Conclusion: The brain network defined by connectivity to positive pons regions might be the regulatory network loop inducing RBD in humans. In addition, our results suggested that the underlying cause of high phenoconversion rate from iRBD to neurodegenerative α-synucleinopathy might be pathological changes in the preclinical stage of α-synucleinopathy located at the regulatory network loop of RBD.
Keywords: Rapid eye movement sleep behavior disorder (RBD); Lesion network mapping; Focal brain lesions; Neuroimage; α-synucleinopathy neurodegenerative diseases

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal skeletal muscle atonia and abnormal behaviors related to dream enactments during REM sleep [1-3]. Abnormal behaviors consist of sleep-related vocalization or complex motor behaviors [4]. Examples of sleep-related vocalization

Received: September 23, 2022 **Revised:** December 18, 2022 **Accepted:** January 8, 2023
Corresponding author: Zhentao Zuo, PhD, State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, 15 Datun Road, Chaoyang District, Beijing 100101, China.
• E-mail: zuozt@ibp.ac.cn; and
Jianguo Xu, MD, PhD, Department of Neurosurgery, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan 610041, China.
• E-mail: xujg@scu.edu.cn

include laughing, gesturing, crying, or singing. Reported complex motor behaviors range from nonspecific repetitive twitching or jerking movements, to violent behaviors, including grabbing, punching, biting, kicking, or leaping from the bed, which can lead to injury or death of self or bedpartner. RBD can be categorized into idiopathic RBD (iRBD) and symptomatic (also known as secondary, such as brainstem tumors, stroke, vascular malformation, etc.) RBD. iRBD is characterized by a lack of definite neurological conditions, and multiple prospective studies have reported that most patients with iRBD will develop α-synucleinopathy neurodegenerative diseases, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2,5-7]. The conversion rate increases significantly with the follow-up duration [8]. Additionally, RBD symptom is frequent in patients with α-synucleinopathy [9]. To date, why iRBD will convert into α-synucleinopathy has not been clearly defined.

Multiple studies have been carried out to identify the neuronal network of REM sleep and the pathogenic mechanisms of RBD [10,11]. In rodents, researchers found that many brain regions might be involved in REM sleep regulation, including the locus coeruleus (LC), sublaterodorsal nucleus (SLD), dorsal raphe nucleus, pedunculopontine nucleus, laterodorsal tegmental nucleus (LDTN), posterior lateral hypothalamus (PH), dorsal paragigantocellular reticular nucleus, ventrolateral periaqueductal gray (VLPAG), thalamus, substantia nigra, basal forebrain, and frontal cortex [3]. Based on animal models in cats and rats, Boeve et al. [4,12] proposed that the SLD nucleus and its afferent or efferent pathways are the most likely pathophysiological basis for RBD, and found that dysfunction of this nucleus or its pathways caused by lesions, neurodegeneration, or pharmacologically-induced dysfunction can result in RBD. In humans, multiple studies reported that patients with lesions, including encephalitis, infarct, hemorrhage, and arteriovenous malformation, in the brainstem and other areas were associated with RBD [13,14]. However, the specific pathogenic mechanisms of RBD in humans are still not clear.

Recently, Fox [15] proposed a technique called lesion network mapping, which can be used to localize neural networks through multiple focal brain lesions causing neurological symptoms. This technique avoids the need to perform functional brain imaging on the patients themselves, and only brain lesion images are needed therein. Lesion network mapping has been applied to a variety of neuropsychiatric symptoms, such as auditory hallucinations, aphasia, pain, hemichorea, parkinsonism, impaired decision-making, memory, freezing of gait, criminality, coma, and free will [15]. Reproducibility and specificity of lesion network mapping has been verified and confirmed accordingly [16,17]. In our study, we intended to localize the neuroanatomical substrate of RBD by applying lesion network mapping to multiple focal brain lesions causing symptomatic RBD and to investigate the neuroanatomical locational relationship between RBD and α-synucleinopathy neurodegenerative diseases.

MATERIALS AND METHODS

Lesion Network Mapping for RBD

Case Selection from the Literature

In our study, PubMed was searched for articles including human RBD participants, which were written in English. The search was done in March 2021 using the following search terms: (Rapid eye movement (REM) sleep behavior disorder (RBD) OR Rapid eye movement sleep behavior disorder (RBD) OR REM sleep behavior disorder) AND (disease OR injury OR lesion OR tumor OR tumour OR stroke OR infarct OR hemorrhage OR haemorrhage OR bleeding OR traumatic) AND (case report OR case series). Initially, 139 studies were found in PubMed. Inclusion criteria were patients with RBD caused by a focal intraparenchymal lesion. Exclusion criteria included: 1) No CT or MRI; 2) extrinsic lesions oppress brain tissue without clearly delineated brain parenchyma damage; 3) poor image resolution and the location or boundary of the lesion could not be determined; 4) RBD without responsible lesions; 5) whole brain lesions and the responsible lesions could not be determined; and 6) genetic diseases leading to extensive brain lesions. After applying these criteria, 13 studies remained and three additional studies were found from a review of their references. Finally, a total of 19 cases were identified from 16 studies (Supplementary Table 1).

Lesion Localization

All brain lesions were mapped by hand onto a standardized human brain atlas (2 x 2 x 2 mm^3 MNI space) according to the CT or MRI images in published studies using MRIcron software (https://people.cas.sc.edu/rorden/mricron/index.HTML). The location of the lesions in the standardized human brain atlas were determined by the anatomical landmarks on the original publication images.

https://doi.org/10.3348/kjr.2022.0712

Korean Journal of Radiology
KJR

Lesion Network Mapping

In the present study, lesion network mapping was applied to investigate the neuroanatomical substrate of RBD. Figure 1 shows the specific experimental process. The specific steps of data analysis refer to previous literature [18,19]. Briefly, the brain lesion of each patient was used as a seed region of interest to calculate the functional connectivity (FC) of the lesion to all brain voxels by calculating the correlated time course between each lesion location and every other brain voxel in a resting-state FC MRI analysis using 1083 healthy subjects' resting-state functional magnetic resonance imaging (fMRI) data from the open access Human Connectome Project (HCP) S1200 data release [20,21]. In our study, the minimized-preprocessing resting-state fMRI data from 1083 healthy subjects were further analyzed including detrend, bandpass filter and global signal regression before calculating FC. In each brain lesion, these correlations for all 1083 subjects were then combined to calculate a *T*-score value for every individual voxel using a one-sample *t* tests. Binarized connectivity maps (positive and negative correlations separately) for each lesion were thresholded at a *T* value of ± 5 (uncorrected $P < 6 \times 10^{-7}$). Finally, binarized connectivity maps from each brain lesion were overlaid to form the lesion network mapping to identify voxels connected to all or most lesion locations associated with RBD. Due to lack of MRI brainstem nuclei template, the positions of brainstem nuclei in this paper were manually drawn on the MRI standard brain template, by referring to the human brainstem atlas [22].

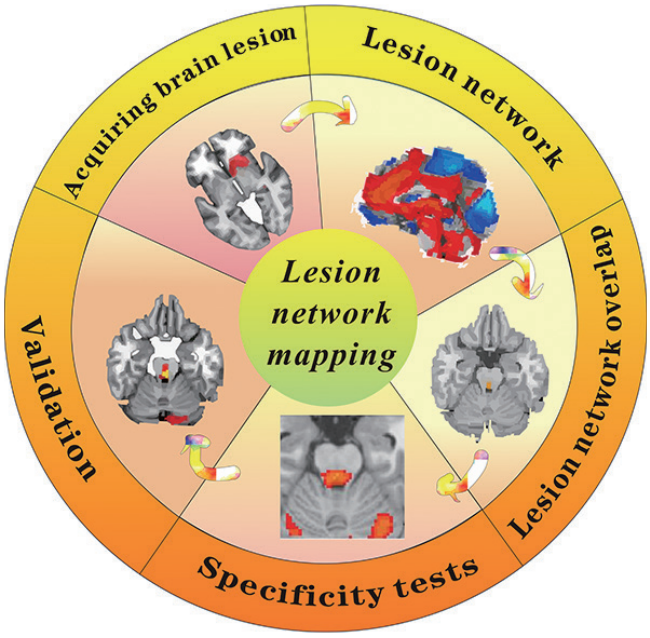

Fig. 1. Scheme. Graphical summary about the lesion network mapping method in the present study.

Comparison with Lesions Causing Other Neurologic Syndromes

To test the specificity of lesion network mapping for RBD, we compared the lesion network mapping results of lesions causing RBD to two 'control' datasets of lesions causing criminal behavior and alien limb syndrome. Seventeen lesions causing criminal behavior, and 50 lesions causing alien limb syndrome, were separately obtained from previously published studies [16,23]. A two-sample *t* test in Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to identify voxels significantly more likely to be connected with lesions causing symptomatic RBD compared to the two control lesions. Voxel-wise family-wise error (FWE) corrected *P* values less than 0.05 were considered significant group differences in the lesion network.

Validation of the Network Localization Using an Independent Group of iRBD Patients

The neuroimaging findings in iRBD were searched in PubMed through articles written in English using the search terms (Rapid eye movement (REM) sleep behavior disorder (RBD) OR Rapid eye movement sleep behavior disorder (RBD) OR REM sleep behavior disorder) AND (MRI or SPECT or PET) in April 2021, by identifying 227 studies. Abnormal brain structure, blood flow or metabolism in iRBD patients compared with healthy controls using PET, SPECT, or structural MRI, such as whole-brain cortical thickness, voxel-based morphometry, or diffusion-tensor imaging analyses, were included accordingly. In each study, functional lesions in iRBD were defined as injury, atrophy, or hypoactivity on functional neuroimaging compared to healthy controls, and the coordinates for functional lesions were extracted therein. A total of 13 studies met the requirements (Supplementary Table 2). All reported coordinates for each individual study were defined as 4-mm seeds and added together to create a combined seed [23]. Then, the combined seed for each study as a lesion was applied to calculate network mapping of iRBD using the identical procedure of lesion network mapping. We also tested the specificity of this network localization to regions involved in iRBD by comparing our results with neuroimaging findings in 13 studies of patients with free will [23]. Two-sample *t* tests in SPM12 were used to assess the group differences in network connectivity using an FWE-corrected *P* value less than 0.05.

https://doi.org/10.3348/kjr.2022.0712

In addition, we investigated whether there were potential brain pathological alterations in iRBD by searching PubMed for articles with human subjects, written in English, using the search terms (autopsy OR histopathologic examination OR postmortem OR post-mortem OR immunohistochemistry OR neuropathological examination) AND (Rapid eye movement (REM) sleep behavior disorder (RBD) OR Rapid eye movement sleep behavior disorder (RBD) OR REM sleep behavior disorder) in April 2021 and found 67 studies. The inclusion criteria were patients with iRBD but with no other neurologic signs or symptoms. Finally, 2 cases met the inclusion criteria. We collected brain pathological sites in these studies (Supplementary Table 3) and verified the relationship between brain pathological alterations in iRBD and lesion network mapping for RBD.

Locational Relationships between Lesion Network Mapping for RBD and Pathological Alteration in α-synucleinopathy Neurodegenerative Diseases

We further investigated the relationships between lesion network mapping for RBD and the brain pathological sites at preclinical stages in α-synucleinopathy, such as PD and DLB. Brain pathological sites at different clinical stages in PD and DLB were obtained from previous studies [5,24]. Then, we detected the match degree of brain pathological sites at preclinical stages in α-synucleinopathy with lesion network mapping of RBD.

Ethics

This study does not contain any activities performed by any of the authors which requires human participants or animals. Data on patients with lesions causing RBD were identified through literature in PubMed. Resting-state fMRI data were from HCP, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657).

RESULTS

Lesions Causing RBD

In our literature search for lesion-induced RBD, we identified 19 lesion locations (mean age 54.5 ± 19.0 years, 15 males) that met our inclusion/exclusion criteria (Supplementary Table 1). The lesion location was heterogeneous and it was distributed in different brain regions, including the pons (n = 12), mesial temporal lobes (n = 3), caudate (n = 1), midbrain (n = 1), thalamus (n = 2), parieto-occipital lobe (n = 1), medulla (n = 1), Ponto-mesencephalic region (n = 2), and amygdala (n = 1) (Fig. 2). Five patients had lesions in multiple locations.

Lesion Network Mapping of RBD

The connectivity mapping of each lesion was calculated using a large database (n = 1083) of resting-state FC from HCP (Fig. 3A, B). Then, lesion network mapping of RBD was created by overlapping the binarized connectivity mapping of each lesion thresholded at a T value of 5 (uncorrected $P < 6 \times 10^{-7}$) (Fig. 3B). Despite heterogeneity in lesion location, 95% of lesion locations (18 of 19 lesions) causing RBD exhibited positive FC to the pons as shown in Figure 3C (cluster size = 34 voxels, peak coordinates X = 0, Y = -29, Z = -20 on MNI152 space). According to the human brainstem template, we found that positive brain regions in the pons covered the LC, dorsal raphe nucleus, central superior nucleus, and VLPAG (Fig. 3D).

Specificity and Validation of Lesion Network Mapping

To assess the specificity of this result, the connectivity pattern specific to lesions causing RBD was separately compared with two control lesions using a two-sample t test in SPM12. Results showed that the pons is a specific brain region involved in RBD (Fig. 4).

In addition, to verify that lesion locations causing RBD are part of a common brain network defined by connectivity to the pons, the connectivity mapping of pons was calculated using a large database (n = 1083) of resting-state FC from HCP (Fig. 5A). The brain network defined by connectivity to the pons aligned with the lesion network mapping was defined by over 68% of lesion locations causing RBD (Fig. 5B, C). More importantly, all lesion locations causing RBD fell within the common brain network defined by connectivity to the pons (Fig. 5D).

Next, we validated the literature-based RBD lesion network map with data from an independent cohort of neuroimaging findings in iRBD relative to healthy controls. Using the same analysis, the lesion network mapping of these 13 studies was calculated (Fig. 6A, B). We found that over 62% (8 of 13) of functional lesions were functionally connected to the pons, which aligned well with the results derived from focal brain lesions (Fig. 6C). The site of the pons was specific for neuroimaging findings reported in patients with iRBD compared with neuroimaging findings from patients with free will (Fig. 6D).

Furthermore, we identified two patients with iRDB who underwent post-mortem. Pathological α-synuclein was found

https://doi.org/10.3348/kjr.2022.0712

Korean Journal of Radiology
KJR

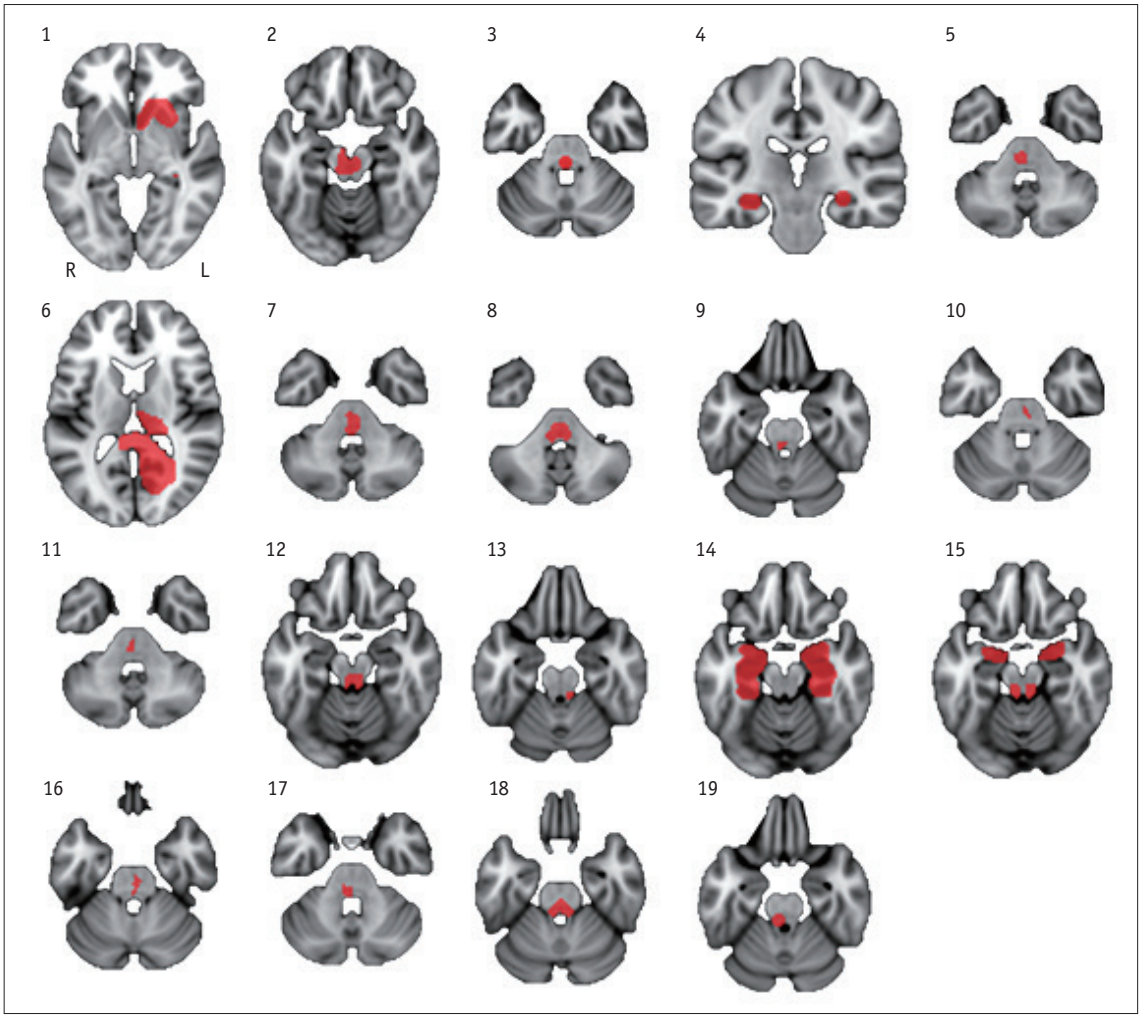

Fig. 2. Lesions causing rapid eye movement sleep behavior disorder (RBD). Lesions from 19 patients with acquired RBD were identified from a systematic literature search or from cases seen by the authors and mapped by hand onto a standardized human brain atlas (2 x 2 x 2 mm^3 MNI space). The red parts indicate the lesions. L = left, R = right

in multiple brain sites in these patients. More importantly, these sites were also located at lesion network mapping for RBD (Supplementary Table 3).

Neuroanatomical Locational Relationship between Network for RBD and α-Synucleinopathy Neurodegenerative Diseases

We detected the locational relationship between the lesion network mapping for RBD and the brain pathological sites at different clinical stages in PD and DLB by overlapping the brain network defined by connectivity to the pons and brain pathological sites at preclinical stages in PD and brainstem Lewy body disease in DLB. In PD, we found that all brain pathological sites (vagal dorsal motor nucleus, lower raphe nuclei, and LC) at preclinical stages (Braak stages 1–2) were involved in the brain network defined by connectivity to the pons (Fig. 7). Similarly, in DLB, we found that all brain pathological sites (vagal dorsal motor nucleus, raphe nuclei, LC, substantia nigra, and pars compacta) at brainstem Lewy body disease were involved in the brain network defined by connectivity to the pons (Fig. 7).

DISCUSSION

In this study, we investigated the brain network of RBD using patient data obtained from systematic literature search and lesion network mapping, which can localize the brain network of lesion-induced symptoms and which has proven useful in the localization of multiple neurological syndromes [15]. Our results showed that more than 89% of the lesions were connected to the pons. By searching the Human Brain Stem Atlas, we found that the positive brain

https://doi.org/10.3348/kjr.2022.0712

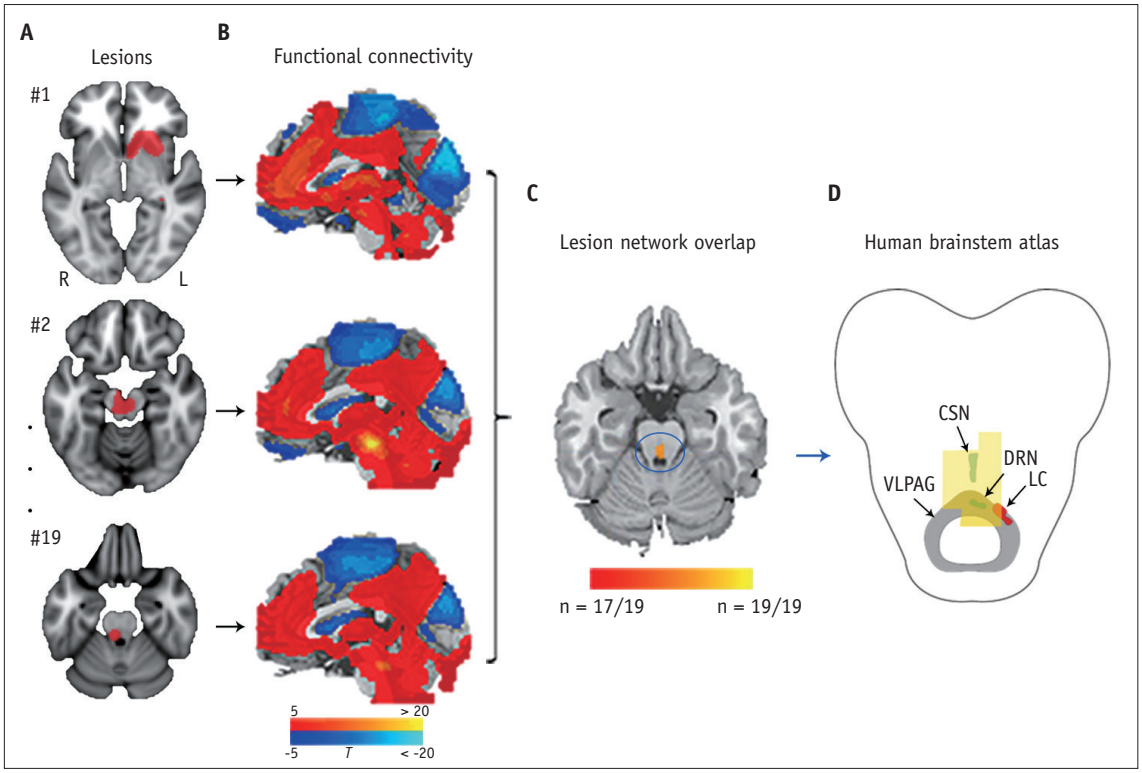

Fig. 3. Lesion network mapping of rapid eye movement sleep behavior disorder (RBD). **A.** Three RBD causing representative lesions. The red parts indicate the lesions. **B.** functional connectivity between each of the three representative lesion location and the rest of the brain across a large (n = 1083) resting-state functional connectivity dataset from Human Connectome Project. **C.** Number of lesion locations functionally connected to each brain voxel. The orange part in circle indicate the survive voxels. **D.** The positive regions map on the human brainstem atlas (left column) to identify the involved nucleus. LC = locus coeruleus, DRN = dorsal raphe nucleus, CSN = central superior nucleus, VLPAG = ventrolateral periaqueductal gray thalamus, L = left, R = right

regions in the pons were located in the LC, dorsal raphe nucleus, central superior nucleus, and VLPAG. To verify the specificity of this result, we compared the FC of lesions causing RBD with that of the two control lesions causing other neurological syndromes. The results showed that these pontine-positive brain regions also survived.

In addition, we validated the literature-based RBD lesion network mapping with data from an independent cohort of functional lesions in iRBD relative to healthy controls. Although these patients did not have focal brain lesions, the regions of focal injury, atrophy or hypoactivity on structural or functional neuroimaging in groups of patients with iRBD were defined as functional lesions. This method conformed to lesion network localization of free will [23]. We found that the sites of pons derived from focal brain lesions aligned well with the results from functional lesions. We further studied whether all the lesions causing RBD were located in the brain network defined by connectivity to the positive pons regions, including the LC, dorsal raphe nucleus, and VLPAG. We used positive pons regions as a seed to calculate whole-brain FC using resting-state fMRI data from 1083 HCP healthy subjects. We found the FC network defined by positive pons regions matched the brain network connectivity to more than 50% of lesions causing RBD. At the same time, all the lesions causing RBD are included in the brain network defined by positive pons regions. In animal experiments, damage to the LC, LDTN, and SLD have been reported to reproduce RBD in humans [11,25,26]. In addition, through experimental studies in rats and cats, the potential pathological circuit of RBD has been proposed [3,12,27]. During REM sleep, γ-aminobutyric acid (GABA)-ergic neurons located in the PH, the dorsal paragigantocellular reticular nucleus, and the VLPAG inactivate REM-inhibiting monoaminergic neurons in the tuberomammillary nucleus, LC, and dorsal raphe nucleus, and GABAergic neurons in the VLPAG to induce REM sleep. SLD glutamatergic/GABAergic neurons stimulate inhibitory spinal interneurons or glycinergic and GABAergic premotor neurons in the ventromedial medulla, resulting in skeletal muscle atonia. SLD neurons may be activated by cholinergic LDTN and pedunculopontine tegmental nucleus neurons.

https://doi.org/10.3348/kjr.2022.0712

Korean Journal of Radiology
KJR

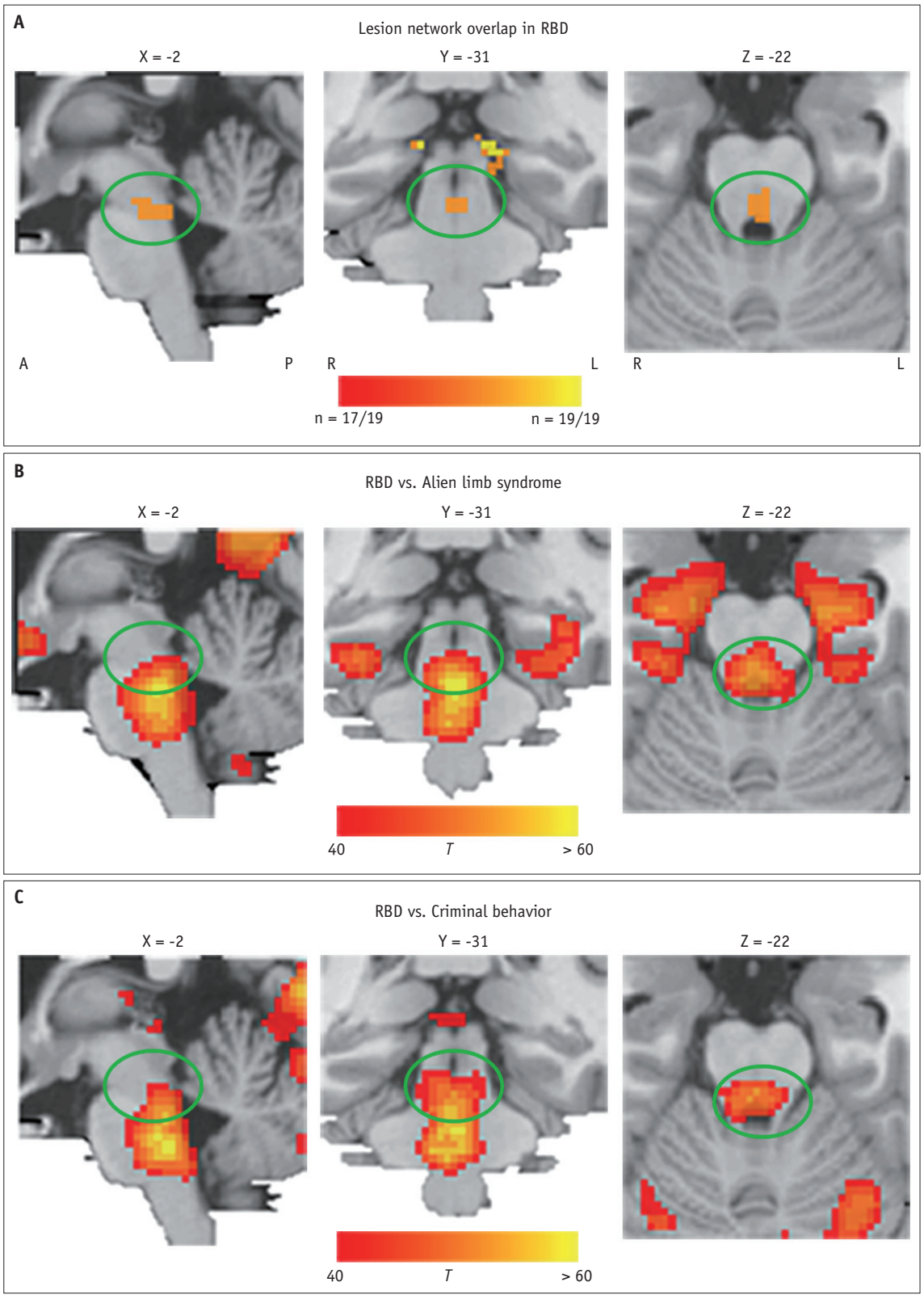

Fig. 4. The specificity of lesion network mapping for rapid eye movement sleep behavior disorder (RBD). **A.** Lesion network overlap mapping showing regions connected to ≥ 18 lesion locations. **B.** Two-sample *t* tests comparing the functional connectivity of lesions causing RBD with lesions causing alien limb syndrome (voxel-wise family-wise error [FWE]-corrected $P < 0.05$). **C.** Two-sample *t* tests comparing the functional connectivity of lesions causing RBD with lesions causing criminal behavior (voxel-wise FWE-corrected $P < 0.05$). The green circles represent the specific regions of RBD relative to other neurological syndromes. A = anterior, P = posterior, L = left, R = right

https://doi.org/10.3348/kjr.2022.0712

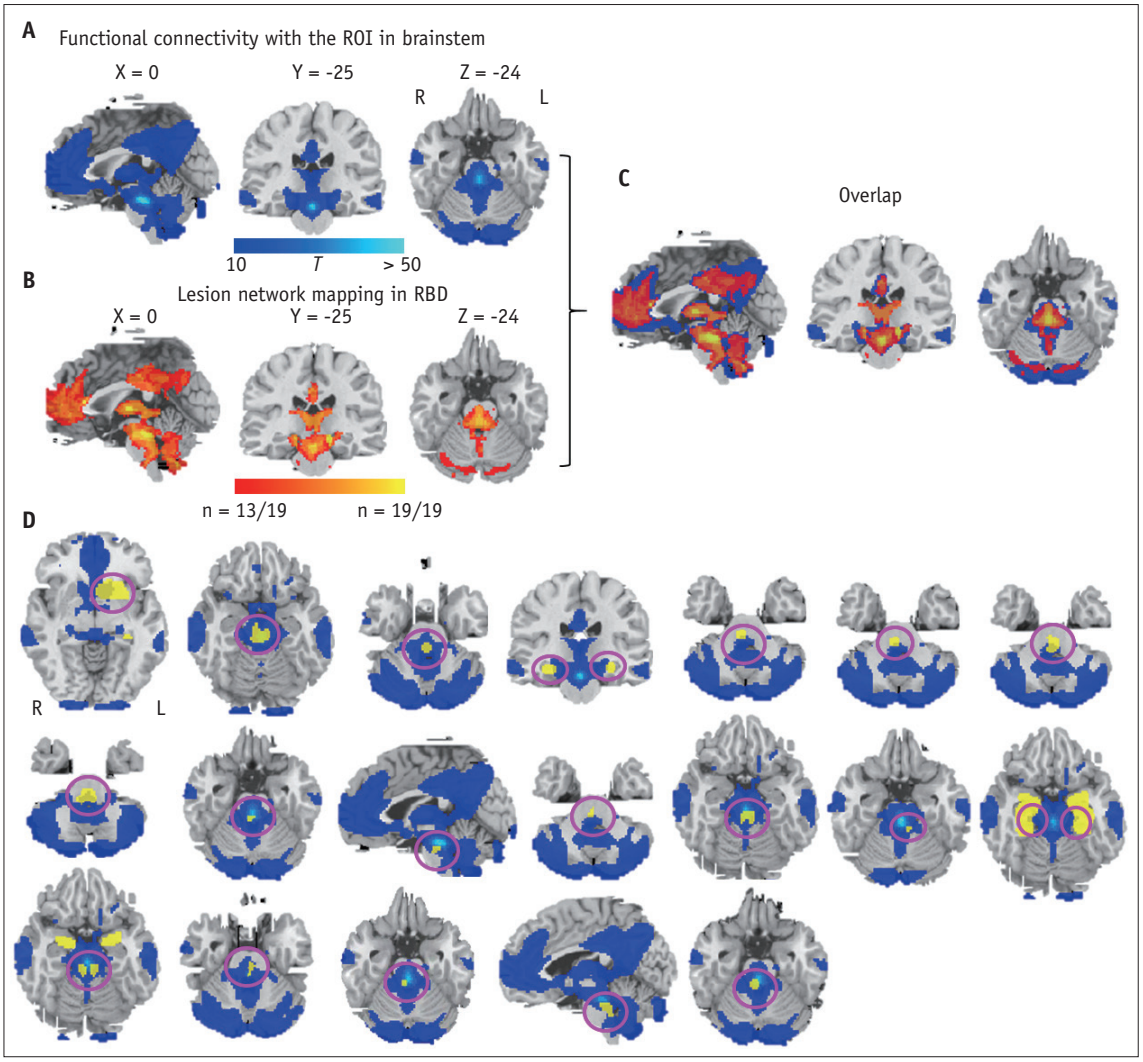

Fig. 5. Brain network defined by the positive regions in the brainstem. **A.** Functional connectivity between the positive regions in the brainstem and the rest of the brain across a large (n = 1083) resting-state functional connectivity dataset from Human Connectome Project. **B.** Lesion network overlap mapping showing regions connected to connectivity to ≥ 13 lesion locations. **C.** The brain network defined by positive regions in the brainstem (blue) overlaps with lesion network mapping defined by connectivity to ≥ 13 lesion locations (red–yellow). **D.** The brain network defined by positive regions in the brainstem (blue) that encompasses all heterogeneous lesion locations causing rapid eye movement sleep behavior disorder (RBD) (yellow, circled in pink). ROI = region of interest, L = left, R = right

Cortical activation during REM sleep is restricted to a few limbic structures, including the retrosplenial cortex, medial entorhinal cortex, anterior cingulate cortex and dentate gyrus. In the present study, we found that all the positive pons regions, including the LC, dorsal raphe nucleus, and VLPAG, are involved in the key brain areas for RBD reported in animals. To further confirm reliability of lesion network map for RBD, we collected the pathological changes in brain sites reported in iRBD post-mortem by a literature search. We identified only two patients with iRBD who underwent autopsy [28,29]. Pathological alterations, including neuronal loss, gliosis, Lewy bodies, and Lewy neurites, were detected mainly in the brain stem nucleus (such as LC, subceruleus nucleus, substantia nigra, dorsal raphe nucleus et al.). As expected, the brain sites of pathological alterations found in two patients with iRBD who underwent autopsy were also involved in lesion network mapping for RBD. Therefore, our findings suggested that the regulatory network loop of RBD in humans may be the brain network defined by connectivity to positive pons regions, including the LC, dorsal raphe nucleus, central superior nucleus, and VLPAG. Taken together, based on the lesion network mapping, we have deepened the understanding of the potential neuroanatomical substrate of RBD, and also made it possible to develop effective

https://doi.org/10.3348/kjr.2022.0712

Korean Journal of Radiology
KJR

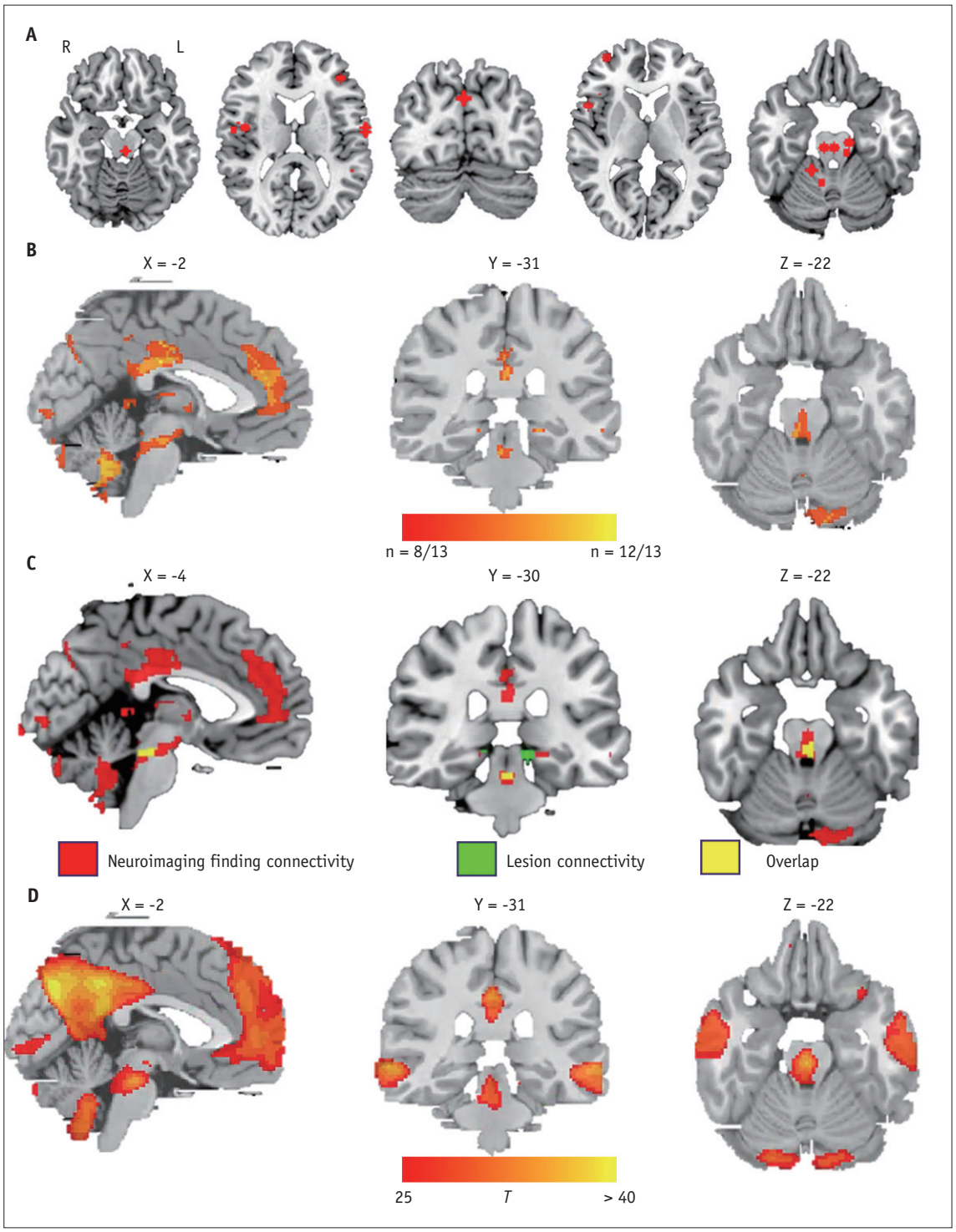

Fig. 6. Brain network of neuroimaging abnormalities in idiopathic rapid eye movement sleep behavior disorder (iRBD). **A.** Coordinates from five representative neuroimaging studies (of 13 total) reporting abnormalities in patients with iRBD. Red parts indicate the coordinate. **B.** Lesion network overlap mapping showing regions connected to ≥ 8 combined seeds. **C.** Lesion network mapping defined by the connectivity to ≥ 18 lesion locations in rapid eye movement sleep behavior disorder (green) overlap with lesion network mapping defined by the connectivity to ≥ 8 combined seeds (red). The yellow regions represent the coincidence area. **D.** Two-sample *t* tests comparing the functional connectivity of coordinates from iRBD with coordinates from free will, a control disorder (voxel-wise family-wise error-corrected $P < 0.05$). L = left, R = right

https://doi.org/10.3348/kjr.2022.0712

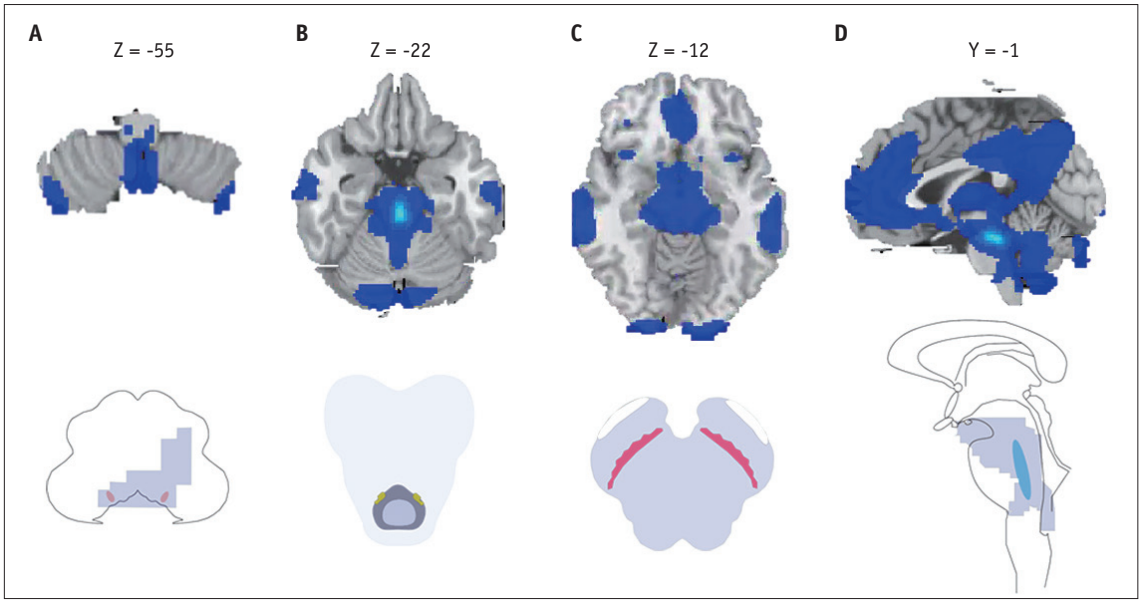

Fig. 7. The locational relationships between lesion network mapping for rapid eye movement sleep behavior disorder (RBD) and brain pathological sites at preclinical stages in α-synucleinopathy. The brain pathological sites at preclinical stages (Braak stages 1–2) in Parkinson's disease and at brainstem Lewy body disease in dementia with Lewy bodies, including the vagal dorsal motor nucleus **(A)**, locus coeruleus **(B)**, pars compacta in the substantia nigra **(C)**, and raphe nucleus **(D)**, were involved in this brain network defined by connectivity to the pons. Below corresponding to the magnetic resonance imaging is the schematic drawings about the nucleus. Light gray represents positive regions in the network of RBD, red in **A** represents vagal dorsal motor nucleus, yellow in **B** represents locus coeruleus, pink in **C** represents pars compacta, bright blue in **D** represents raphe nucleus.

RBD diagnostic methods and therapeutic and prognostic evaluation methods from the aspect of functional imaging.

The most important implication of iRBD is its high phenoconversion to α-synucleinopathy neurological disease, including PD, DLB, and MSA. However, the underlying cause is still unclear. In the present study, based on the finding of regulatory network loop of RBD by lesion network mapping, we investigated the locational relationship between network loop of RBD and the brain location of pathological changes in the preclinical stage of α-synucleinopathy. We found that all brain pathological sites at preclinical stages (Braak stages 1–2) in PD and at brainstem Lewy body disease in DLB fell within the brain network defined by connectivity to the pons. In DLB staging, the determination of preclinical stage is controversial, but pure brainstem pathological changes cannot lead to the typical clinical manifestations of DLB [30]. In addition, in an autopsy study of multiple studies, with a large sample of PD patients, researchers found that PD patients with probable RBD may have a greater density and range of synuclein pathology in the LC, substantia nigra, cranial nerve nuclei IX/X, and basal amygdala, all of which fall within the brain network defined by connectivity to the pons [31]. To summarize, we determined that pathological changes in the early stage of α-synucleinopathy neurodegenerative diseases were located in the regulatory network loop of RBD, thus resulting in iRBD. This may explain why iRBD is highly transformed into α-synucleinopathy. With the development of brain pathological changes, the clinical features of PD, DLB, MSA, or other neurodegenerative diseases will gradually appear. Clinically, iRBD should be diagnosed early, and its etiology should be clarified subsequently. Patients with iRBD caused by α-synucleinopathy neurodegenerative diseases should be treated early to delay or block the progression of brain pathological changes in them.

Our study is limited since several potential limitations of the lesion network mapping technique have been identified and addressed in previous studies [16,18,32,33]. First, all lesion information comes from published images, which may be biased due to the impact of image quality when drawing lesion maps. Second, we do not have our own patient queue to further verify our experimental results. Furthermore, in the present study, specific positive nuclei or regions in the brainstem could not be reported due to the lack of a human brainstem nuclei atlas in MRI. To identify specific nuclei or regions in the brain stem, we compared the positive regions at the different brainstem levels with the human brainstem template, which may have some deviations.

In conclusion, the brain network defined by connectivity

https://doi.org/10.3348/kjr.2022.0712

Korean Journal of Radiology
KJR

to positive pons regions may be the regulatory network loop inducing RBD in humans. In addition, our results suggest that the underlying cause of high phenoconversion rate from iRBD to neurodegenerative α-synucleinopathy may be pathological changes in the preclinical stage of α-synucleinopathy located at the regulatory network loop of RBD.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0712.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article and its supplementary information files.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Data curation: Taoyang Yuan, Zhentao Zuo. Formal analysis: Taoyang Yuan, Zhentao Zuo. Funding acquisition: all authors. Investigation: Taoyang Yuan, Zhentao Zuo. Methodology: Taoyang Yuan, Zhentao Zuo. Project administration: Jianguo Xu. Resources: Taoyang Yuan, Zhentao Zuo. Software: Taoyang Yuan, Zhentao Zuo. Supervision: Jianguo Xu. Validation: Taoyang Yuan, Zhentao Zuo. Visualization: Taoyang Yuan, Zhentao Zuo. Writing—original draft: Taoyang Yuan, Zhentao Zuo. Writing—review & editing: Jianguo Xu.

ORCID iDs

Taoyang Yuan
https://orcid.org/0000-0003-0173-5722
Zhentao Zuo
https://orcid.org/0000-0002-5909-3884
Jianguo Xu
https://orcid.org/0000-0001-9651-8186

Funding Statement

This work was financially supported by the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC18007), the Ministry of Science and Technology of China grant (2020AAA0105601), the University Synergy Innovation Program of Anhui Province, China (GXXT-2021-002), the Youth Innovation Promotion Association CAS (2021091), and the Post-Doctor Research Project, West China Hospital, Sichuan University (2021HXBH063).

Acknowledgments

Data were provided in part by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

REFERENCES

1. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146:1387-1394
2. Dauvilliers Y, Schenck CH, Postuma RB, Iranzo A, Luppi PH, Plazzi G, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers* 2018;4:19
3. Zhang F, Niu L, Liu X, Liu Y, Li S, Yu H, et al. Rapid eye movement sleep behavior disorder and neurodegenerative diseases: an update. *Aging Dis* 2020;11:315-326
4. Rodriguez CL, Jaimchariyatam N, Budur K. Rapid eye movement sleep behavior disorder: a review of the literature and update on current concepts. *Chest* 2017;152:650-662
5. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443-453
6. Postuma RB, Iranzo A, Hogl B, Arnulf I, Ferini-Strambi L, Manni R, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. *Ann Neurol* 2015;77:830-839
7. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* 2013;14:744-748
8. Galbiati A, Verga L, Giora E, Zucconi M, Ferini-Strambi L. The risk of neurodegeneration in REM sleep behavior disorder: a systematic review and meta-analysis of longitudinal studies. *Sleep Med Rev* 2019;43:37-46
9. St Louis EK, Boeve AR, Boeve BF. REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Mov Disord* 2017;32:645-658
10. Boucetta S, Cissé Y, Mainville L, Morales M, Jones BE. Discharge profiles across the sleep-waking cycle of identified cholinergic, GABAergic, and glutamatergic neurons in the pontomesencephalic tegmentum of the rat. *J Neurosci* 2014;34:4708-4727

11. Valencia Garcia S, Libourel PA, Lazarus M, Grassi D, Luppi PH, Fort P. Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder. *Brain* 2017;140:414-428
12. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 2007;130(Pt 11):2770-2788
13. Iranzo A, Graus F, Clover L, Morera J, Bruna J, Vilar C, et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. *Ann Neurol* 2006;59:178-181
14. Iranzo A, Aparicio J. A lesson from anatomy: focal brain lesions causing REM sleep behavior disorder. *Sleep Med* 2009;10:9-12
15. Fox MD. Mapping symptoms to brain networks with the human connectome. *N Engl J Med* 2018;379:2237-2245
16. Darby RR, Horn A, Cushman F, Fox MD. Lesion network localization of criminal behavior. *Proc Natl Acad Sci U S A* 2018;115:601-606
17. Laganiere S, Boes AD, Fox MD. Network localization of hemichorea-hemiballismus. *Neurology* 2016;86:2187-2195
18. Boes AD, Prasad S, Liu H, Liu Q, Pascual-Leone A, Caviness VS Jr, et al. Network localization of neurological symptoms from focal brain lesions. *Brain* 2015;138(Pt 10):3061-3075
19. Corp DT, Joutsa J, Darby RR, Delnooz CCS, van de Warrenburg BPC, Cooke D, et al. Network localization of cervical dystonia based on causal brain lesions. *Brain* 2019;142:1660-1674
20. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, et al. The WU-Minn Human Connectome Project: an overview. *Neuroimage* 2013;80:62-79
21. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* 2013;80:105-124
22. Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM. *Duvernoy's atlas of the human brain stem and cerebellum*, 1st ed. Vienna: Springer, 2009:95-96
23. Darby RR, Joutsa J, Burke MJ, Fox MD. Lesion network localization of free will. *Proc Natl Acad Sci U S A* 2018;115:10792-10797
24. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. *Lancet Neurol* 2009;8:1150-1157
25. George R, Haslett WL, Jenden DJ. A Cholinergic mechanism in the brainstem reticular formation: induction of paradoxical sleep. *Int J Neuropharmacol* 1964;3:541-552
26. Roussel B, Buguet A, Bobillier P, Jouvet M. [Locus ceruleus, paradoxal sleep, and cerebral noradrenaline]. *C R Seances Soc Biol Fil* 1967;161:2537-2541. French
27. Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM sleep at its core - circuits, neurotransmitters, and pathophysiology. *Front Neurol* 2015;6:123
28. Boeve BF, Dickson DW, Olson EJ, Shepard JW, Silber MH, Ferman TJ, et al. Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med* 2007;8:60-64
29. Uchiyama M, Isse K, Tanaka K, Yokota N, Hamamoto M, Aida S, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology* 1995;45:709-712
30. Marui W, Iseki E, Kato M, Akatsu H, Kosaka K. Pathological entity of dementia with Lewy bodies and its differentiation from Alzheimer's disease. *Acta Neuropathol* 2004;108:121-128
31. Postuma RB, Adler CH, Dugger BN, Hentz JG, Shill HA, Driver-Dunckley E, et al. REM sleep behavior disorder and neuropathology in Parkinson's disease. *Mov Disord* 2015;30:1413-1417
32. Darby RR, Laganiere S, Pascual-Leone A, Prasad S, Fox MD. Finding the imposter: brain connectivity of lesions causing delusional misidentifications. *Brain* 2017;140:497-507
33. Cohen AL, Fox MD. Reply: the influence of sample size and arbitrary statistical thresholds in lesion-network mapping. *Brain* 2020;143:e41

https://doi.org/10.3348/kjr.2022.0712