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MINI-REVIEW

Brain Functional Connectivity Changes in Rapid Eye Movement Sleep Behavior Disorder

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The idiopathic rapid eye movement sleep behavior disorder (iRBD) has been reported as prodromal biomarker for neurodegenerative synucleinopathies. To early detect neurodegeneration in preclinical stage, pathophysiological changes of iRBD have been studied in many ways including structural magnetic resonance imaging (MRI), functional MRI (fMRI), and connectivity analyses. This review summarizes functional connectivity studies using resting-state fMRI in iRBD patients focused on motor-related network, compensatory mechanism of synucleinopathies, cognitive dysfunction, and non-motor symptoms.

Keywords: idiopathic RBD; Functional connectivity; Resting-state fMRI

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INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behaviors associated with loss of normal muscle atonia during REM sleep [1]. The idiopathic RBD (iRBD) has been reported as prodromal biomarker for neurodegenerative synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy [2]. To early detect neurodegeneration in preclinical stage, pathophysiological changes of iRBD have been studied for two decades. Brain structural studies using magnetic resonance imaging (MRI) in iRBD patients suggested alterations in cortical and subcortical volume [3-8].

The brain works as a network of different brain regions that each have their own function. The anatomical connectivity is the physical connections or interactions between two anatomical area and can be studied with structural imaging in collaboration with diffusion tensor tractography methods [9]. In the past few years, novel neuroimaging techniques and analysis methods have enabled the examination of brain functional connectivity (FC) that defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions [10-12].

The resting-state functional MRI (fMRI) was first reported by Biswal et al. [13], showing brain is not silent even during the resting or relaxing state [11,13]. They showed presence of synchronous low-frequency fluctuations of signal intensities from the resting human brain that have a high degree of temporal correlation both within and across the sensorimotor cortex. And they suggested blood oxygenation level dependent signals play a dominant role in the mechanism that gives rise to FC in the resting human brain. Since then, several similar studies have shown other FC in primary visual network, auditory network, and cognitive networks [14-18]. This review summarizes the existing research on the FC studies in iRBD patients focused on resting-state fMRI.

RESTING-STATE fMRI STUDIES IN iRBD PATIENTS

We searched in the PubMed database for literature using resting-state fMRI in patients with iRBD. Keywords were "(resting-state functional magnetic resonance imaging OR resting-state fMRI) AND (rapid eye movement sleep behavior disorder OR REM sleep behavior disorder OR RBD)." A total number of 39 studies were searched, and we excluded studies that were not written in English; reviews; not related to our main topic. After removing, selected articles were 13 (Table 1).

Methodologically, voxel-based connectivity analyses were applied in 11 reviewed studies [19-29] and node-based connectivity analyses were applied in 2 studies [30,31]. The voxel-based analyses models estimate FC values between specific regions of interest and all the other voxels in the whole brain, performing the spatial organization of large-scale resting-state networks. The node-base analyses are graph-based connectivity models represented by two concepts: node (i.e., different brain areas) and edges (i.e., connections between considered regions) [32].

Early two studies, using a voxel-based analysis, showed FC change in networks involving substantia nigra [19] and basal ganglia [20]. These results served as evidence that resting-state fMRI studies could be used as an early biomarker for synucleinopathies, but it was unclear whether they were a result of damaged connectivity by synucleinopathy pathology. There were follow-up studies that also showed abnormalities in motor-related networks using another analysis method like regional homogeneity (ReHo) and independent component analyses (ICA) [22,24,25].

In the preclinical stage of synucleinopathies like PD, compensatory mechanisms may take place to delay the clinical onset of motor symptoms by counteracting nigrostriatal dysfunction. Basal ganglia, cortical premotor areas, thalamus, and cerebellum had been suggested as key regions in those mechanisms [28,33-35]. Recently, some studies showed that there were FC changes related in the PD compensatory mechanisms. Byun et al. [21] showed increased FC between the left thalamus and occipital regions and Chen et al. [28] reported higher amplitude of low-frequency fluctuations (ALFF) values in right parahippocampal gyrus that was already known association with iRBD in positron emission tomography FC study [36].

iRBD is often accompanied by cognitive decline involving executive, visuospatial, attention, and memory functions [37]. A pioneering study by Rolinski et al. [20] showed that FC change did not correlate with changes in cognitive function. But many recent studies using other analyses methods showed FC change in cognitive related brain regions including thalamo-fusiform FC [21], striatal-prefrontal FC [25], striatal-cortical FC [26], and nucleus basalis of Meynert with the left lateral occipital cortex and lingual gyrus [27]. And these results were correlated with neurocognitive results.

The pathophysiology of PD non-motor symptoms is not yet clear. Recently, several studies showed FC changes related in non-motor symptoms such as olfactory and autonomic dysfunction. Chen et al. [28] reported negative correlation between olfactory function and ALFF in right superior occipital gyrus. Woo et al. [29] showed hypoconnectivities with the left olfactory cortex and left amygdala, increased functional connectivity with the left gyrus rectus. FC change related to autonomic dysfunction was reported by Li et al. [24]. They showed reduced functional connectivity between the brainstem and the cerebellum posterior lobe, temporal lobe and anterior cingulate. And these FC findings were negatively correlated with the Scales for Outcomes in Parkinson's Disease-Autonomic scores.

Table 1. Summary of 13 studies about functional connectivity using resting-state fMRI in RBD patients

Study (author, year)	Number of subject (patient/control)	Age (yr) of patient/control	Number of male subject (patient/control)	Imaging modality	Covariates
Ellmore et al. (2013) [19]	10/11	57.0±2.7/57.0±2.4	6/4	Voxel (seed-to-seed)	-
Rolinski et al. (2016) [20]	26/23	67.0±7.7/60.5±8.9	22/5	Voxel (ICA)	-
Campabadal et al. (2020) [30]	20/27	71 (10.0)/66.5 (13.0) median (interquartile range)	14/13	Node (graph theory)	Age, sex, head motion
Li et al. (2020) [22]	33/32	64.91±7.74/63.33±5.25	19/14	Voxel (Seed-to-seed)	Age, sex, FD
Li et al. (2020) [23]	15/15	64.27±1.87/64.80±1.83	9/9	Voxel (ReHo/ALFF)	Age, sex, years of education
Li et al. (2021) [24]	33/38	63.76±7.97/63.03±5.52	21/18	Voxel (ICA)	Age, sex
Byun et al. (2020) [21]	37/15	67.7±7.1/68.3±3.3	25/9	Voxel (Seed-to-seed)	Age, sex, years of education
Wakasugi et al. (2021) [25]	50/70	69.4±5.6/68.7±6.2	35/38	Voxel (ICA)	Age, sex, medication for RBD
Zhang et al. (2021) [26]	21/22	64 (9.5)/60 (8.0) median (interquartile range)	14/9	Voxel (Seed / ReHo)	Age, sex, education
Byun et al. (2022) [27]	20/20	70.6±3.6/68.1±3.4	12/11	Voxel (seed to voxel)	Age, sex, education level
Chen et al. (2022) [28]	27/33	65.89±8.54/68.25±7.80	19/20	Voxel (ALFF)	Age, sex
Geng et al. (2022) [31]	21/22	61.00±10.68/60.27±7.60	14/9	Node (graph theory)	Age, sex, education
Woo et al. (2023) [29]	51/39	70.24±5.95/69.51±5.12	29/11	Voxel (seed to voxel)	Age, sex

fMRI, functional magnetic resonance imaging; RBD, rapid eye movement sleep behavior disorder; FC, functional connectivity; ICA, independent component analyses; FD, framewise displacement; ReHo, regional homogeneity; ALFF, amplitude of low-frequency fluctuations

CONCLUSIONS

As the aging population increases, the prevention and treatment of neurodegenerative diseases is important. Identifying brain changes in iRBD patients, known as a prodromal biomarker of synucleinopathies, gives us much important evidence for early treatment in preclinical stage. Because the brain works in a network system, structural and functional connectivity studies are important in neuropsychological disease. In future study, longitudinal designs are needed to know the temporal and causal relations between FC changes and conversion to synucleinopathies.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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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REFERENCES

1. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 2002;25:120-138.
2. 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.
3. Campabadal A, Segura B, Junque C, Serradell M, Abos A, Uribe C, et al. Cortical gray matter and hippocampal atrophy in idiopathic rapid eye movement sleep behavior disorder. Front Neurol 2019;10:312.
4. Hanyu H, Inoue Y, Sakurai H, Kanetaka H, Nakamura M, Miyamoto T, et al. Voxel-based magnetic resonance imaging study of structural brain changes in patients with idiopathic REM sleep behavior disorder. Parkinsonism Relat Disord 2012;18:136-139.
5. Park KM, Lee HJ, Lee BI, Kim SE. Alterations of the brain network in idiopathic rapid eye movement sleep behavior disorder: structural connectivity analysis. Sleep Breath 2019;23:587-593.
6. Pereira JB, Weintraub D, Chahine L, Aarsland D, Hansson O, Westman E. Cortical thinning in patients with REM sleep behavior disorder is associated with clinical progression. NPJ Parkinsons Dis 2019;5:7.
7. Rahayel S, Postuma RB, Montplaisir J, Génier Marchand D, Escudier F, Gaubert M, et al. Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder. Neurology 2018;90:e1759-e1770.
8. Ellmore TM, Hood AJ, Castriotta RJ, Stimming EF, Bick RJ, Schiess MC. Reduced volume of the putamen in REM sleep behavior disorder patients. Parkinsonism Relat Disord 2010;16:645-649.
9. Smitha KA, Akhil Raja K, Arun KM, Rajesh PG, Thomas B, Kapilamoorthy TR, et al. Resting state fMRI: a review on methods in resting state connectivity analysis and resting state networks. Neuroradiol J 2017;30:305-317.
10. Aertsen AM, Gerstein GL, Habib MK, Palm G. Dynamics of neuronal firing correlation: modulation of "effective connectivity." J Neurophysiol 1989;61:900-917.
11. Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993;13:5-14.
12. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20:519-534.
13. Biswal BB, Van Kylen J, Hyde JS. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed 1997;10:165-170.
14. Cordes D, Haughton V, Carew JD, Arfanakis K, Maravilla K. Hierarchical clustering to measure connectivity in fMRI resting-state data. Magn Reson Imaging 2002;20:305-317.
15. Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, et al. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 2000;21:1636-1644.
16. Damoiseaux JS, Greicius MD. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct Funct 2009;213:525-533.
17. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700-711.
18. Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 1998;7:119-132.
19. Ellmore TM, Castriotta RJ, Hendley KL, Aalbers BM, Furr-Stimming E, Hood AJ, et al. Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. Sleep 2013;36:1885-1892.
20. Rolinski M, Griffanti L, Piccini P, Roussakis AA, Szewczyk-Krolikowski K, Menke RA, et al. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. Brain 2016;139(Pt 8):2224-2234.
21. Byun JI, Kim HW, Kang H, Cha KS, Sunwoo JS, Shin JW, et al. Altered resting-state thalamo-occipital functional connectivity is associated with cognition in isolated rapid eye movement sleep behavior disorder. Sleep Med 2020;69:198-203.
22. Li G, Chen Z, Zhou L, Yao M, Luo N, Kang W, et al. Abnormal intrinsic brain activity of the putamen is correlated with dopamine deficiency in idiopathic rapid eye movement sleep behavior disorder. Sleep Med 2020;75:73-80.
23. Li G, Zhou L, Chen Z, Luo N, Niu M, Li Y, et al. Dynamic functional connectivity impairments in idiopathic rapid eye movement sleep behavior disorder. Parkinsonism Relat Disord 2020;79:11-17.
24. Li G, Chen Z, Zhou L, Zhao A, Niu M, Li Y, et al. Altered structure and functional connectivity of the central autonomic network in idiopathic rapid eye movement sleep behaviour disorder. J Sleep Res 2021;30:e13136.
25. Wakasugi N, Togo H, Mukai Y, Nishikawa N, Sakamoto T, Murata M, et al. Prefrontal network dysfunctions in rapid eye movement sleep behavior disorder. Parkinsonism Relat Disord 2021;85:72-77.
26. Zhang HJ, Wang SH, Bai YY, Zhang JW, Chen S. Abnormal striatal-cortical networks contribute to the attention/executive function deficits in idiopathic rem sleep behavior disorder: a resting state functional MRI study. Front Aging Neurosci 2021;13:690854.
27. Byun JI, Cha KS, Kim M, Lee WJ, Lee HS, Sunwoo JS, et al. Association of nucleus basalis of meynert functional connectivity and cognition in idiopathic rapid-eye-movement sleep behavior disorder. J Clin Neurol 2022;18:562-570.
28. Chen M, Li Y, Chen J, Gao L, Sun J, Gu Z, et al. Structural and functional brain alterations in patients with idiopathic rapid eye movement sleep behavior disorder. J Neuroradiol 2022;49:66-72.
29. Woo KA, Kim H, Yoon EJ, Shin JH, Nam H, Jeon B, et al. Brain olfactory-related atrophy in isolated rapid eye movement sleep behavior disorder. Ann Clin Transl Neurol 2023;10:2192-2207.
30. Campabadal A, Abos A, Segura B, Serradell M, Uribe C, Baggio HC, et al. Disruption of posterior brain functional connectivity and its relation to cognitive impairment in idiopathic REM sleep behavior disorder. Neuroimage Clin 2020;25:102138.

31. Geng C, Wang S, Li Z, Xu P, Bai Y, Zhou Y, et al. Resting-state functional network topology alterations of the occipital lobe associated with attention impairment in isolated rapid eye movement behavior disorder. Front Aging Neurosci 2022;14:844483.
32. Fasiello E, Gorgoni M, Scarpelli S, Alfonsi V, Ferini Strambi L, De Gennaro L. Functional connectivity changes in insomnia disorder: a systematic review. Sleep Med Rev 2022;61:101569.
33. Binkofski F, Reetz K, Gaser C, Hilker R, Hagenah J, Hedrich K, et al. Morphometric fingerprint of asymptomatic Parkin and PINK1 mutation carriers in the basal ganglia. Neurology 2007;69:842-850.
34. van Nuenen BF, Weiss MM, Bloem BR, Reetz K, van Eimeren T, Lohmann K, et al. Heterozygous carriers of a Parkin or PINK1 mutation share a common functional endophenotype. Neurology 2009;72:1041-1047.
35. Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain 2013;136(Pt 3):696-709.
36. Ge J, Wu P, Peng S, Yu H, Zhang H, Guan Y, et al. Assessing cerebral glucose metabolism in patients with idiopathic rapid eye movement sleep behavior disorder. J Cereb Blood Flow Metab 2015;35:2062-2069.
37. Jozwiak N, Postuma RB, Montplaisir J, Latreille V, Panisset M, Chouinard S, et al. REM sleep behavior disorder and cognitive impairment in Parkinson's disease. Sleep 2017;40:zsx101.