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 for 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>
<thead>
<tr>
<th>Study (author, year)</th>
<th>Number of subject (patient/control)</th>
<th>Age (yr) of patient/control</th>
<th>Imaging modality</th>
<th>Number of male subject (patient/control)</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellmore et al. (2013) [19]</td>
<td>10/11</td>
<td>57±2.7/57±2.4</td>
<td>Voxel (seed-to-seed)</td>
<td>6/4</td>
<td>-</td>
</tr>
<tr>
<td>Rolinski et al. (2016) [20]</td>
<td>26/23</td>
<td>67±7.1/60±5.8</td>
<td>Voxel (ICA)</td>
<td>19/14</td>
<td>-</td>
</tr>
<tr>
<td>Campabadal et al. (2020) [30]</td>
<td>20/27</td>
<td>71 (10)/66.5 (13.9)</td>
<td>Node (graph theory)</td>
<td>14/13</td>
<td>Age, sex, head motion</td>
</tr>
<tr>
<td>Li et al. (2020) [21]</td>
<td>33/32</td>
<td>64.9±7.4/63.3±5.0</td>
<td>Voxel (seed-to-seed)</td>
<td>19/14</td>
<td>-</td>
</tr>
<tr>
<td>Li et al. (2020) [22]</td>
<td>15/15</td>
<td>64.27±1.87/64.80±1.83</td>
<td>Voxel (Seed-to-seed)</td>
<td>9/9</td>
<td>Age, sex, years of education</td>
</tr>
<tr>
<td>Li et al. (2021) [23]</td>
<td>33/38</td>
<td>67.74±6.83±1.5</td>
<td>Voxel (Seed-to-seed)</td>
<td>21/18</td>
<td>Age, sex, education level</td>
</tr>
<tr>
<td>Byun et al. (2022) [24]</td>
<td>20/20</td>
<td>70.24±5.96/75.15±5.12</td>
<td>Voxel (seed to voxel)</td>
<td>14/9</td>
<td>Age, age, sex</td>
</tr>
<tr>
<td>Zhang et al. (2021) [25]</td>
<td>25/23</td>
<td>70.6±3.6/69.5±2.7</td>
<td>Voxel (ICA)</td>
<td>12/11</td>
<td>Age, sex, education level</td>
</tr>
<tr>
<td>Byun et al. (2021) [26]</td>
<td>20/22</td>
<td>64.89±5.46/63.85±5.30</td>
<td>Node (graph theory)</td>
<td>19/20</td>
<td>Age, sex, education level</td>
</tr>
<tr>
<td>Geng et al. (2022) [27]</td>
<td>21/22</td>
<td>61.00±10.68/60.27±7.60</td>
<td>Voxel (Seed / ReHo)</td>
<td>14/9</td>
<td>Head motion, medication for RBD</td>
</tr>
<tr>
<td>Woo et al. (2023) [28]</td>
<td>51/39</td>
<td>69.5±6.48/75.15±5.12</td>
<td>Voxel (Seed to voxel)</td>
<td>21/22</td>
<td>Age, sex, education level</td>
</tr>
</tbody>
</table>

fMRI, functional magnetic resonance imaging; RBD, rapid eye movement sleep behavior disorder; FC, functional connectivity; ICA, independent component analyses; FD, framewise displacement.
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.

CONCLUSIONS


17. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700-711.


