Background and Objective
Mild motor dysfunction is a strong predictor of Parkinson's disease or dementia with Lewy bodies in RBD patients. It is speculated that the RBD patients with subtle motor dysfunction had developed a pre-clinical neurodegenerative. The objective of this study is to investigate whether RBD patients with subtle motor dysfunction have already started nigrostriatal dopaminergic dysfunction and corticostriatal network alteration by using 123I-FP-CIT SPECT and resting state fMRI.

Subjects
Patients
N=18 (7 males and 11 females, 71±4 years)
Psychomotor-confirmed RBD: N=16 (6 males)
Probable RBD: N=2 (1 male)
No motor complaint, UPDRS part III ≤5
Healthy controls (HC)
N=20 (13 males and 7 females, 70±4 years)
No neurological or psychological disorder

Table 1: Polysomnographic measures (RBD vs HC)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBD</td>
<td>HC</td>
</tr>
<tr>
<td>EEE (3h)</td>
<td>92 ± 12</td>
<td>90 (89-92)</td>
</tr>
<tr>
<td>Sleep duration (min)</td>
<td>400 ± 60</td>
<td>380 (360-440)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>21 ± 11</td>
<td>24 (18-26)</td>
</tr>
<tr>
<td>Sleep (min)</td>
<td>250 ± 30</td>
<td>240 (230-260)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>89 ± 5</td>
<td>88 (86-90)</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>320 ± 20</td>
<td>310 (290-330)</td>
</tr>
<tr>
<td>REM sleep (min)</td>
<td>100 ± 20</td>
<td>98 (96-102)</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>30 ± 5</td>
<td>28 (25-32)</td>
</tr>
<tr>
<td>Rapid eye movement</td>
<td>60 ± 10</td>
<td>60 (50-70)</td>
</tr>
<tr>
<td>Percent REM sleep (%)</td>
<td>20 ± 3</td>
<td>19 (15-23)</td>
</tr>
<tr>
<td>Stage 1 sleep</td>
<td>7 ± 2</td>
<td>7 (6-8)</td>
</tr>
<tr>
<td>Stage 2 sleep</td>
<td>18 ± 3</td>
<td>17 (15-20)</td>
</tr>
<tr>
<td>Stage 3 sleep</td>
<td>10 ± 2</td>
<td>10 (9-12)</td>
</tr>
<tr>
<td>Stage 4 sleep</td>
<td>9 ± 2</td>
<td>9 (7-11)</td>
</tr>
<tr>
<td>Stage 5 sleep</td>
<td>1 ± 0</td>
<td>1 (0-1)</td>
</tr>
</tbody>
</table>

Methods-1
Finger tapping
Instructed to tap index finger and thumb as rapidly and widely as possible. Recorded with a motor sensing device for 15s. Corrected by Maximal distance (MD) between index finger and thumb.

Classification of RBD Patients
RBD with Subtle motor dysfunction (RBD-S) n=7
At least one in six parameters abnormal using cut-off 2SD
RBD with “normal” motor function (RBD-N) n=11
The other RBD patients with values inside of 2SD for all the above parameters

Methods-2
123I-FP-CIT SPECT
Scanner: dual-head gamma camera with a high-resolution fan beam collimator
Volumes of interest (VOI): caudate, anterior putamen, posterior putamen
Data analysis: SPM8
- Specific binding ratio (SBR) = [(R-L)/(R+L)]
- Latency index = [(R-L)/(R+L)]
- Caudate : Putamen ratio = Posterior putamen binding (R+L)

Group comparison: ANOVA with post hoc Tukey, P values <0.05

Brain MRI
MRI scanner: 3T Siemens Skyra
EPI: TR 2500ms/TE 30ms, flip angle 80°, resolution 3 x 3 x 3mm, FOV 142 mm, 39 slices
MPRAGE: TR 2300ms/TE 2.96ms, flip angle 9°, voxel size 1 x 1 x 1mm, FOV 256mm, 176 slices
Image processing and analysis for resting state fMRI: software (CONN-CONN toolbox)
- 1. Entire BOLD time courses extracted from following seed regions and averaged.
- 2. Fisher-z-transformation applied to convert the resting correlation coefficients.
- 3. Individual functional connectivity maps put into a random effects analysis.
- ROI-to-ROI analysis conducted.
- 4. Group comparison conducted (FDR adjusted P values <0.05).

Correlation analysis (in RBD)
The correlation between finger tapping and 123I-FP-CIT uptake (Pearson’s correlation coefficient)
Regression analysis between functional connectivity and finger tapping or 123I-FP-CIT uptake

Discussion
Resting state fMRI
Our result might show a part of cortico-striatal network alteration precedes clinical onset of Parkinson’s disease or DLB. In previous research, resting state functional changes in the basal ganglia network were reported in RBD patients before the onset of clinically relevant motor symptoms.

Correlation analysis
The resting state functional connectivity between right M1 and right caudate might be important for finger tapping amplitude in RBD. The resting state functional connectivity between posterior putamen and sensori-motor cortex might be altered early along with mild nigrostriatal dopaminergic dysfunction. The possible reasons of no correlation between finger tapping performance and 123I-FP-CIT uptake may be less severe striatal dopaminergic dysfunction than Parkinson’s disease or the contribution of non-dopaminergic dysfunction.

Conclusion
The RBD patients with subtle motor dysfunction had nigrostriatal dopaminergic and cortico-striatal network alteration.
Corticostriatal follow-up is necessary to investigate whether subtle motor dysfunction defined using finger tapping is a risk of developing synucleinopathies.

References
1) Postuma et al., Neurology 2015; 84: 1104-13
2) Oishi et al., J Neurol Sci 2007; 256: 52-60
3) Agostino et al., Mov Disord 2003; 18: 560-5
4) Walker et al., Neurology 2004; 62: 1568-72
5) Irazoqui et al., Lancet Neurol 2010; 9: 1070-7
6) Irazoqui et al., Ann Neurol 2011
7) Rolski et al., Brain 2016; 139: 2224-34

COI Disclosure
Name of presenter: Gohei Yamada
Nagoya University has conducted collaborative research with Hitachi Ltd. The device used in this study was leased to Nagoya City University by Hitachi Ltd.
123I-FP-CIT was provided as DATSCAN (MetrPhysics, Tokyo, Japan).

Discussion-1
Finger tapping
In previous study of finger tapping, lower amplitude and slowness during flexion were revealed in Parkinson’s disease compared with healthy controls. The RBD-S group showed the findings similar to Parkinson’s disease. However, there were only two RBD patients with abnormal motor asymmetry. The RBD-S group may include not only preclinical Parkinson’s disease but also preclinical DLB.

123I-FP-CIT SPECT
The lower SBR in the posterior putamen, the higher laterality index of SBR in the posterior putamen and the higher caudate:putamen ratio are the findings similar to Parkinson’s disease. In RBD, nigrostriatal dopaminergic dysfunction is one of predictors of synucleinopathies.

Results-1
1) Finger tapping
Mean ± SD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RBD-S</th>
<th>RBD-N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Open Speed</td>
<td>7.6 (3.2)</td>
<td>5.9 (3.7)</td>
</tr>
<tr>
<td>Mean Peak Open Speed</td>
<td>13.6 (2.4)</td>
<td>12.6 (2.8)</td>
</tr>
<tr>
<td>Mean Peak Close Speed</td>
<td>22.0 (2.6)</td>
<td>20.2 (2.9)</td>
</tr>
<tr>
<td>Mean %Amplitude</td>
<td>13.8 (2.4)</td>
<td>12.5 (2.9)</td>
</tr>
<tr>
<td>Mean Amplitude Index</td>
<td>0.2 (0.1)</td>
<td>0.3 (0.2)</td>
</tr>
</tbody>
</table>

2) Clinical characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>HC</th>
<th>RBD-S</th>
<th>RBD-N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72 (3.5)</td>
<td>71 (1.8)</td>
<td>71 (1.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Gender</td>
<td>15 (75%)</td>
<td>11/4 (69)</td>
<td>11/6 (59)</td>
<td>0.46</td>
</tr>
<tr>
<td>Education</td>
<td>11 (55)</td>
<td>11 (55)</td>
<td>15 (65)</td>
<td>0.33</td>
</tr>
<tr>
<td>Marital status</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (10)</td>
<td>0.21</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>N/A</td>
<td>4.0 (2.0)</td>
<td>4.1 (2.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>4.1 (1.0)</td>
<td>5.0 (1.0)</td>
<td>3.1 (1.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>HGS</td>
<td>28.0 (17)</td>
<td>28.1 (17)</td>
<td>28.5 (17)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data shown are mean (SD), N/A: not applicable. *P<0.05, UPDRS-III: United Parkinson’s Disease Rating Scale, M1: Motor Exper. Examination.

Results-2
4) Resting state fMRI
ROI analysis conducted.

The functional connectivity between caudate and SPL or S1 was significantly reduced in the RBD-S group. The functional connectivity between posterior putamen and S1 was significantly reduced in the RBD-N group.

5) Correlation analysis (in RBD)
There was no correlation 123I-FP-CIT uptake and finger tapping.

(b) The lower mean SBR in posterior putamen was associated with the stronger functional connectivity between left posterior putamen and sensori-motor cortex.

(a) The lower mean %Amplitude was associated with the stronger functional connectivity between M1 and Caudate.

The SBR in the posterior putamen was significantly lower and the Laterality index in the posterior putamen and the Caudate:Putamen ratio were significantly higher in RBD-S group than HC group.