Neural synchronization analysis of electroencephalography coherence in patients with Parkinson’s disease-related mild cognitive impairment

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ABSTRACT

Introduction: The underlying pathophysiology of slight cognitive dysfunction in Parkinson’s disease-related mild cognitive impairment (PD-MCI) is yet to be elucidated. Our study aimed to evaluate the association between cognitive function and brain functional connectivity (FC) in patients with PD-MCI.

Methods: Twenty patients with sporadic PD-MCI were evaluated for FC in the brain network. Further, electroencephalography (EEG) coherence analysis in the whole-brain and quantified regional coherence using phase coupling were performed for each frequency, and motor and cognitive function were assessed in the whole-brain.

Results: The degree of cognitive impairment was related to a decrease in the coherence in the alpha ranges. The regional coherence in the left frontal-left parietal region rather than the right frontal-right parietal region showed a higher correlation with the cognitive function scores.

Conclusion: The differences in EEG coherence across different types of cognitive dysfunction reflect a compensatory response to the heterogeneous and complex clinical presentation of PD-MCI. Our findings indicate decreased brain efficiency and impaired neural synchronization in PD-MCI; these results may be crucial in elucidating the pathological exacerbation of PD-MCI.

1. Introduction

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases characterized by motor and non-motor symptoms. Cognitive dysfunction is one of the many non-motor symptoms, and its eventual progression to dementia is a common complication in a large proportion of patients with PD. PD-related mild cognitive impairment (PD-MCI) is a prodromal stage of PD with dementia. Cognitive dysfunction has been described in the context of disease progression and has a major impact on the quality of life of patients with PD. However, the underlying mechanisms of cognitive impairment in PD-MCI patients have not been well recognized.

Quantitative analyses of brain rhythms measured using electroencephalography (EEG) provide not only spectral information of cortical rhythms, but also additional data on regional connectivity and whole-brain connectivity. EEG coherence analysis has been used in evaluating functional connectivity (FC) in the cortex as well as other established methods (esupp. Table 1) [1–8]. Therefore, is an indicator of PD severity, since abnormal FC is considered a compensatory mechanism of the brain. Previous studies have compared FC in patients with PD and in healthy controls; however, the association between FC and cognitive dysfunction across PD-MCI and MCI without Parkinsonism has not yet been reported. Our study aimed to explore the association between FC and cognitive dysfunction in patients with PD-MCI.

Abbreviations: PD, Parkinson’s disease; MCI, Mild Cognitive Impairment; FC, functional connectivity; RBD, rapid eye movement sleep behavior disorder; EEG, electroencephalography; MMSE, Mini-Mental State Examination; MDS-UPDRS, Movement Disorder Society Unified Parkinson’s Disease Rating Scale; HDS-R, Revised Hasegawa Dementia Score; FAB, Frontal Assessment Battery; MCI, mild cognitive impairment; FF, frontal-frontal; TT, temporal-temporal; FT, frontal-temporal; PO, parietal-occipital; PF, parietal-frontal; FPL, left frontal-left parietal; FPR, right frontal-right parietal; LEDD, levodopa-equivalent daily dose.

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2. Materials and methods

2.1. Patients

Patients with sporadic PD and MCI without Parkinsonism, who visited the Nara Medical University Hospital, Nara, Japan, between May 2013 and February 2022, were enrolled. Based on the assumptions outlined in the previous case series [9], a total of 20 PD-MCI patients fulfilled the inclusion and exclusion criteria. Twelve PD-MCI patients were excluded (esupp. Fig. 1). MCI without Parkinsonism fulfilled all criteria except the inclusion criteria 1).

The major inclusion criteria were as follows:

- Japanese patients with confirmed PD, who met the UK PD Society Brain Bank criteria.
- Patients with memory-related complaints, no significant levels of impairment in other cognitive domains, essential preservation of daily living activities, and without dementia.
- Patients with a Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive).
- Patients with a clinical dementia rating (CDR) above 0.5.
- Patients who were capable of ambulatory hospital visits.
- Patients who provided written informed consent.

We excluded subjects if they met any of the following exclusion criteria:

- Patients who had taken drugs such as antianxiety and psychotropic drugs (which could influence EEG readings) or hormonal agents, within 48 weeks before the EEG examination was performed.
- Patients who had undergone surgeries such as deep brain stimulation.
- Patients with a past history of epileptic attack.
- Patients with an implantable ICD or pacemaker.
- Patients with severe mental disorders.
- Patients who had received intervention in other clinical trials or were part of clinical trials within 6 months before the agreement acquisition.

Ethical approval for this study was obtained from the Nara Medical University Clinical Research Ethics Board. All study procedures were performed in accordance with the ethical standards laid by this institutional research committee, the Helsinki declaration, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. All participants signed an informed consent statement after receiving information about the study both verbally and in writing.

2.2. Acquisition protocols

Cognitive function was assessed using the MMSE, Revised Hasegawa Dementia Score (HDS-R), and Frontal Assessment Battery (FAB) [10]. MMSE scores were divided into five subscales, “orientation”, “memory”, “language”, “attention”, and “visuospatial ability”. Motor and non-motor symptoms were measured using the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS).

EEG examinations were performed using the international 10-20 electrode placement system for EEG (Neurofax EEG-1224, Nihon Kohden, Tokyo, Japan). EEG data were obtained with the patients in a supine position. EEG was recorded at a sampling rate of 200 Hz, and electrodes were referenced to linked earlobes (A1 + A2). EEG examinations and cognitive assessments were performed while the medication was “ON” and within 1 month on separate days.

2.3. EEG data processing

After recording, the data were imported into MATLAB version R2020a (Math Works, 2020) and were preprocessed using the EEGLAB v14.1.2 toolbox [11]. EEG data were band-pass filtered with finite impulse response filtering. Low-pass filtering with a cut-off frequency at 45 Hz and high-pass filtering with a cut-off frequency at 1 Hz were applied. Because EEGs were often contaminated with artifacts immediately after recording, we visually selected 60-s resting states starting 5 min after the eyes-closed EEG data was collected, for preprocessing. Data were segmented into 2-s epochs, and artifact-contaminated EEG epochs were removed. Time-frequency and coherence analyses were performed using the newcrosf function in EEGLAB. Frequency analyses were performed across all electrodes (16 channels) using the fast Fourier transformation algorithm with wavelet transformation and a frequency resolution of 1 Hz. EEG data were analyzed separately in four frequency bands [12]. The notch filter was used at 50 Hz for data. EEG signals were decomposed using wavelet transformation that applied two cycles per frequency band (theta, alpha, beta, and gamma).

2.4. Whole-brain coherence and regional coherence

Whole-brain coherence and regional coherence were calculated based on the coherence of all electrode pairs. Whole-brain coherence was calculated by averaging the coherence values of all electrode pairs for each frequency band [13]. In total, 120 electrode pairs were assigned to the following eight region types: frontal-frontal (FF), temporal-temporal (TT), frontal-temporal (FT), parietal-occipital (PO), parietal-temporal (PT), frontal-parietal (FP), left frontal-left parietal (FPL), and right frontal-right parietal (FPR). Regional coherence was calculated by averaging the coherence values of electrode pairs between the region for each frequency band.

2.5. Statistical analyses

Statistical analyses were performed using SPSS version 22.0 (SPSS Japan, Tokyo, Japan) and MATLAB version R2020a. The Shapiro–Wilk test was used to assess the normality of data distribution. Correlations between the cognitive test scores and coherence values were assessed using Spearman’s correlation coefficient. A correlation coefficient ($r$) > 0.45 was defined as a strong correlation, and that between 0.45 and 0.35 was defined as a slight correlations. $P$-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

We enrolled 20 sporadic PD-MCI patients (age; 72.7 ± 8.4, sex; 12 male/8 female, disease duration; 6.3 ± 3.1 years, H-Y stages; 3.0 ± 0.8, levodopa-equivalent daily dose [LEDD]; 609.8 ± 382.8 mg, MDS-UPDRS Total; 57.6 ± 28.5, Part I; 12.1 ± 7.0, Part II; 15.1 ± 10.2, Part III; 25.3 ± 13.4, Part IV; 5.1 ± 3.7, MMSE score; 26.4 ± 1.9, HDS-R score; 25.5 ± 3.2, FAB score; 13.7 ± 2.2) and 10 MCI patients without Parkinsonism (age; 70.4 ± 5.6, sex; 6 male/4 female) (mean ± SD) (Table. 1). The coherence values of whole-brain, FF, FT, FP, FPL, and FPR in PD-MCI were smaller than that in MCI without Parkinsonism.

3.2. Relationship between EEG coherence and clinical characteristics

Whole-brain coherence did not show a correlation with the disease duration, age, or LEDD. On the other hand, there were strong correlations with MDS-UPDRS total score ($r = -0.577$), Part I ($r = -0.534$), and Part II ($r = -0.606$). Whole-brain coherence showed a slight correlation with Part III ($r = -0.402$). The correlation with whole-brain coherence is shown in Fig. 1 A-H. FPL and FPR coherence values were...
A correlation analysis was performed between EEG whole-brain coherence in the alpha range and the MMSE, HDS-R, and FAB scores (supple Table 2). MMSE scores showed a correlation with whole-brain coherence \( r = 0.761 \). There were also correlations between whole-brain coherence and FAB scores \( r = 0.560 \) as well as HDS-R scores \( r = 0.620 \). EEG regional coherence (FF, FP, FPL, FPR, PT, FT, PO, and TT) in the alpha range was calculated based on the coherence values. A correlation analysis was also performed between MMSE total scores and regional coherence. There were correlations between MMSE total scores and regional coherences. Regional coherence in the FP region showed a correlation with whole-brain coherence, such as orientation and attention. A previous study based on magnetic resonance imaging (MRI) reported impaired connectivity between the frontal and parietal brain regions in PD with dementia [1]. Our results indicated laterality of FC in relation to MMSE total scores. It is also noteworthy that regional coherence in the FPL region showed a higher correlation with the scores of cognitive function than that in the FPR region. Furthermore, the regional coherence in FPL was only correlated with memory-related items. The patients with PD with cognitive impairment showed lower connectivity in the left frontal-parietal network than healthy participants and PD patients without cognitive impairment [1]; another study revealed the relationship between left frontal-parietal coherence and executive function in PD [17]. Altogether, the disrupted connectivity in the left frontal-parietal cortex might indicate cognitive dysfunction in PD. Cognitive dysfunction in PD-MCI might be caused by long-term potentiation in the left frontal-parietal cortices. This hypothesis is also supported by the pathological finding of \( \alpha \)-synuclein accumulation in the frontal lobe from an early stage of the disease [18].

In this study, we presented a novel approach to evaluate the mechanism in PD-MCI using EEG coherence analysis. These results may be significant in elucidating the mechanism of cognitive function in PD. However, our results should be interpreted with caution based on the following limitations. First, this was a pilot study with a limited sample size and only cross-sectional study design. Based on the pilot study results, a large clinical trial will be needed to validate these results in appropriate populations. Second, the symptomatology of PD is recognized to be rather heterogeneous, with various clinically significant features and laterality. In the analysis of motor symptoms, it is therefore necessary to analyze not only alpha waves but also fast waves [19]. Third, measurements were performed only at one time-point, and Lewy pathology in PD progresses temporally and spatially through the subsequent neurodegenerative stages of PD. Fourth, all patients did not receive anticholinergic medication, though they did receive anti-parkinsonian medication, which has been reported to influence resting brain activity in PD. Hence, the medication status of patients must be considered when comparing results across studies. Finally, the classified tool of MCI used MMSE in this study: MMSE was sensitive to detecting dementia, however early detection required the modifications; accordingly, our results need to be revalidated using new MCI diagnostic criteria.

4. Discussion

The severity of cognitive impairment was found to be correlated with desynchronization in the alpha bands and reduced network integration [14]. In line with the progression of PD pathology, \( \alpha \)-synuclein aggregates lead to the loss of dopaminergic, serotonergic, and other neurons and can promote the involvement of other brain regions by altering their connectivity [15]. FC analysis has provided new insights regarding the alteration of brain functional networks derived from PD pathology. Braak’s hypothesis suggested that Lewy body deposition, predominantly composed of \( \alpha \)-synuclein, propagates from the brainstem to the cerebral cortex with disease progression. Within the cerebral hemispheres, Lewy body deposition spreads from the frontal lobe to the parietal and occipital lobes. Aberrant deposition of \( \alpha \)-synuclein in cortical lesions is involved in brain dysfunction and causes cognitive impairment [16]. Cognitive scores in this experiment correlated with whole-brain and regional coherences. Regional coherence in the FP region showed a correlation with cognitive dysfunction, such as orientation and attention. A previous study based on magnetic resonance imaging (MRI) reported impaired connectivity between the frontal and parietal brain regions in PD with dementia [1]. Our results indicated laterality of FC in relation to MMSE total scores. It is also noteworthy that regional coherence in the FPL region showed a higher correlation with the scores of cognitive function than that in the FPR region. Furthermore, the regional coherence in FPL was only correlated with memory-related items. The patients with PD with cognitive impairment showed lower connectivity in the left frontal-parietal network than healthy participants and PD patients without cognitive impairment [1]; another study revealed the relationship between left frontal-parietal coherence and executive function in PD [17]. Altogether, the disrupted connectivity in the left frontal-parietal cortex might indicate cognitive dysfunction in PD. Cognitive dysfunction in PD-MCI might be caused by long-term potentiation in the left frontal-parietal cortices. This hypothesis is also supported by the pathological finding of \( \alpha \)-synuclein accumulation in the frontal lobe from an early stage of the disease [18].

In this study, we presented a novel approach to evaluate the mechanism in PD-MCI using EEG coherence analysis. These results may be significant in elucidating the mechanism of cognitive function in PD. However, our results should be interpreted with caution based on the following limitations. First, this was a pilot study with a limited sample size and only cross-sectional study design. Based on the pilot study results, a large clinical trial will be needed to validate these results in appropriate populations. Second, the symptomatology of PD is recognized to be rather heterogeneous, with various clinically significant features and laterality. In the analysis of motor symptoms, it is therefore necessary to analyze not only alpha waves but also fast waves [19]. Third, measurements were performed only at one time-point, and Lewy pathology in PD progresses temporally and spatially through the subsequent neurodegenerative stages of PD. Fourth, all patients did not receive anticholinergic medication, though they did receive anti-parkinsonian medication, which has been reported to influence resting brain activity in PD. Hence, the medication status of patients must be considered when comparing results across studies. Finally, the classified tool of MCI used MMSE in this study: MMSE was sensitive to detecting dementia, however early detection required the modifications; accordingly, our results need to be revalidated using new MCI diagnostic criteria.

5. Conclusions

The EEG analysis in this study revealed decreased brain efficiency...
and impaired neural synchronization in PD-MCI. Brain networks analysis based on EEG coherence might be a potential indicator of the pathological exacerbation of PD-MCI and may be applied to therapeutic methods based on changes in the brain network. Our results were obtained in a pilot study with several limitations and should be interpreted with caution. By using various neuroimaging and neurophysiological techniques, further longitudinal and large-sample studies are needed to elucidate the underlying mechanisms of PD-MCI.

6. Data availability

The data that support the findings of this study are available from the
corresponding author upon reasonable request.

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**CRediT authorship contribution statement**

Tomoo Mano: Conceptualization, Methodology, Software, Writing – original draft, Funding acquisition. Kaoru Kinugawa: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft. Maki Ozaki: Validation, Data curation. Hiroshi Kataoka: Writing – review & editing. Kazuma Sugie: Supervision, Project administration.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2022.100140.

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