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Effect of striatal dopamine depletion on cognition in de novo Parkinson's disease

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ABSTRACT

Introduction: To investigate the relationship between the sub-regional pattern of striatal dopamine depletion and cognitive impairment in early-stage Parkinson's disease (PD), and determine the effect of striatal dopamine density on cognitive prognosis.

Methods: Patients with drug-naïve non-demented PD were divided into mild cognitive impairment (PD-MCI; n = 129) and cognitively normal (PD-CogN; n = 182) groups. Using quantification of the dopamine transporter (DAT) availability in each striatal sub-region with ^{18}F-FP-CIT PET scans, we performed inter-group comparative analysis of DAT availability and multivariate linear regression analysis to assess the association between DAT availability and cognitive performance. Additionally, the effect of baseline DAT availability on the cognitive decline across time as well as on changes in the cognitive status was estimated.

Results: The PD-MCI group exhibited more severely decreased DAT availability in all the striatal sub-regions compared to the PD-CogN group, although there was no significant difference in PD duration. The DAT availability in the caudate, anterior putamen, and ventral striatum was directly associated with attention/working memory, frontal/executive, and visuospatial functions, while the DAT availability of the posterior putamen was not. However, the baseline DAT availability of the striatal sub-regions did not influence the cognitive decline or cognitive status in the longitudinal cognitive assessment.

Conclusion: Our results suggest that striatal DAT availability may determine MCI in patients with de novo PD. Dopamine loss in the associative and limbic striatum is closely linked to cognitive deficits in early-stage PD, although it does not affect cognitive prognosis.

1. Introduction

Cognitive impairment frequently occurs even in the early stages of Parkinson's disease (PD). Although the neurobiology underlying early cognitive changes in PD is still under investigation, dysregulation in neurotransmitter systems has long been described as an important contributor. In particular, the loss of dopamine, the main neurochemical disturbance in PD, occurs prior to changes in the other neurotransmitters [1], and executive dysfunction secondary to dopamine deficiency in fronto-striatal circuits is the earliest cognitive impairment in PD [2]. Cools et al. proposed a 'dopamine overdose' theory to account for the findings that frontal/executive functions recruiting the dorsal striatum was improved by dopaminergic medications whereas reversal learning and impulse control related to less depleted striatal regions were impaired [3]. Thus, dopamine is likely to be a key neurotransmitter that initiates cognitive deficits in the early stages of PD.

Several studies have reported a significant relationship between nigrostriatal dopaminergic denervation, especially in the caudate, and cognitive dysfunction mainly in frontal/executive performance [4–7]. In addition, a recent study showed that the dopamine transporter (DAT) availability in the caudate is an important determinant of PD-related cognition, discriminating mild cognitive impairment (MCI) from the cognitively normal (CogN) status [8]. However, these studies were limited by their small sample size,

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possible confounding effects of dopaminergic medication, limited cognitive batteries, inaccurate determination of striatal DAT availability due to less detailed segmentation of the striatum, and a lack of information on DAT-dependent long-term prognosis of cognitive performance. In the present study, we performed quantitative analysis of DAT availability in the striatal sub-regions with a more detailed segmentation of ^{18}F-FP-CIT PET scans in patients with drug-naïve non-demented PD, and analyzed the DAT availability according to the cognitive status at the time of diagnosis. Additionally, we assessed the relationship between DAT availability in each striatal sub-region and the level of cognitive performance as well as the rate of cognitive decline.

2. Methods

2.1. Subjects

We reviewed the database of the Yonsei Parkinson Center (676 consecutive patients with drug-naïve PD who visited the Movement Disorders and Dementia outpatient clinic at Severance Hospital, Yonsei University Health System from April 2009 to September 2015). PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank. The ^{18}F-FP-CIT PET scans were performed, and all the subjects showed decreased DAT availability in the posterior putamen. There was no evidence of focal brain lesions, diffuse white matter hyperintensities, multiple lacunes in the basal ganglia, or hydrocephalus on brain MRI. Of these, 339 patients underwent a detailed neuropsychological assessment and an ^{18}F-FP-CIT PET scan within a 1-year period, and 28 patients who were initially diagnosed with dementia were excluded from this study to avoid the inclusion of patients with dementia with Lewy bodies. Finally, a total of 311 non-demented PD patients was enrolled in the present study (Fig. S1): The non-demented PD group consisted of patients with PD with MCI (PD-MCI; n = 129) and CogN PD subjects (PD-CogN; n = 182). PD-MCI was diagnosed according to the Movement Disorder Society Task Force guidelines [9]. PD-CogN was diagnosed when a subject showed impairment on less than two items of the detailed neuropsychological test. Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS- III). Olfactory function was measured by the cross-cultural smell identification test (CCSIT), and depression was evaluated by the Beck Depression Inventory (BDI). We classified PD patients as the tremor-dominant or postural instability/gait difficulty (PIGD) clinical phenotypes based on their UPDRS scores. This study was approved by the Yonsei University Severance Hospital institutional review board.

2.2. Neuropsychological assessment

The Seoul Neuropsychological Screening Battery (SNSB), a comprehensive neuropsychological test battery in the Korean language, was administered in all the subjects (Supplementary Methods). The scores on each cognitive domain were classified as abnormal when they were below the 1.5 standard deviation of the age-, sex-, and education-specific norms of 447 normal subjects. Two tests were designated to represent each of the four cognitive domains, except language, as described in our previous work and a diagnosis of PD-MCI was made if impairments on at least two tests were demonstrated [10]. The subjects showed no evidence of abnormalities in the activities of daily living (ADL), judged both clinically and on an instrumental ADL scale.

2.3. Quantitative analysis of the ^{18}F-FP-CIT PET images

We used the same methodology to obtain and analyze the ^{18}F-FP-CIT PET images as previously described (Supplementary Methods) [11].

2.4. Longitudinal assessment of the effects of baseline DAT availability on cognitive decline across time

Of the 311 non-demented PD patients, 96 patients underwent serial neuropsychological assessment 2–4 times with the interval of 1–4 years (Fig. S1). We assessed the effect of baseline DAT availability on the cognitive decline across time with a linear mixed model. Additionally, we also compared the baseline DAT availability between the cognitively stable and worsened patients with non-demented PD in the longitudinal cognitive assessment. The subjects were classified into the cognitively worsened group when they were subsequently diagnosed as having an advanced cognitive status, i.e., conversion to PD with dementia (PDD) in patients with PD-MCI, or conversion to PD-MCI or PDD in patients with PD-CogN. The subjects who subsequently showed a similar cognitive performance were classified into the cognitively stable group. The levodopa equivalent dose (LED) [12] for each subject at the last follow-up neuropsychological assessment was compared between the groups.

2.5. Statistical analyses

To compare the baseline demographic characteristics between the patients with PD-MCI and PD-CogN, Student's *t*-tests and Pearson's χ^2 tests were used for continuous and categorical variables, respectively. To compare the neuropsychological test subscores between the non-demented PD groups, an analysis of covariance (ANCOVA) was used while adjusting for age, sex, and years of education as covariates. We also compared the composite scores, calculated by dividing the sum of z-scores by the number of tests in each cognitive domain, in a detailed neuropsychological test. The comparison of DAT availability of each striatal sub-region among the non-demented PD groups was performed using an ANCOVA that included age, sex, PD duration, years of education, and UPDRS-III as covariates. A multivariate linear regression analysis was used to test the association between a composite score of each cognitive domain and DAT availability adjusted for sex. The false discovery rate (FDR) controlling method was used for multiple comparisons correction. A linear mixed model was used to evaluate the change in cognitive decline over time. Three fixed effects were included in the model: two between-subjects effects, namely baseline DAT availability and age; and one within-subject effect, namely time. Subject was considered as a random effect. The effect of the baseline DAT availability on cognitive decline across time was tested using the time x DAT availability interaction term. The statistical analyses were performed with SPSS (version 23.0; IBM Corporation, Armonk, NY, USA), and results with a two-tailed $P < 0.05$ were considered statistically significant.

3. Results

3.1. Demographic characteristics of patients with PD-MCI and PD-CogN

The average age and age at onset of parkinsonism were both higher in the PD-MCI group than in the PD-CogN group. The sex and PD duration of the two groups were not significantly different. Patients with PD-MCI were less educated, had higher UPDRS-III and BDI scores, and had lower Korean version of the Mini-Mental State Examination (K-MMSE) and CCSIT scores than those in the PD-CogN group. There were no significant differences in motor subtypes between the PD-MCI and PD-CogN groups. The PD-MCI group

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