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Research Article

Apathy in Alzheimer's Disease Correlates with the Dopamine Transporter Level in the Caudate Nuclei

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Keywords
Alzheimer's disease · Apathy · Caudate nucleus · Dementia · Single-photon emission computed tomography

Abstract
Introduction: Apathy is a common neuropsychiatric symptom in patients with Alzheimer's disease (AD). The striatal binding potential (BP) of ^{123}I-FP-CIT (*N*-δ-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]tropane) single-photon emission computed tomography (SPECT) is correlated with the degree of apathy in patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB). This study aimed to determine if dopaminergic activity in the basal ganglia is associated with the development of apathy in AD. ***Methods:*** Nineteen subjects with AD were included and underwent ^{123}I-FP-CIT-SPECT. Patients with other types of dementia as a comorbidity, those taking antidepressants, and those with overt parkinsonism were excluded. Apathy was assessed using the Apathy Evaluation Scale Informant-Japanese version (AES-I-J). SPECT images were overlaid with images in striatal regions of interest (ROIs), and the SPECT values in these regions were counted. The relationship between BP values and AES-I-J scores was investigated using Spearman's rank correlation coefficient. ***Results:*** Significant inverse correlations were observed between BP values and AES-I-J scores in the left caudate nucleus and there was a marginally significant inverse correlation in the right caudate nucleus. ***Conclusion:*** The pathological basis of apathy might be the impairment of the dopaminergic nervous system. Further studies on more subjects with AD, healthy controls, and patients with PD and DLB are needed.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that accounts for 60–80% of all subtypes of dementia [1]. Previous research has demonstrated that 88% of patients with AD have neuropsychiatric symptoms [2] and that it is these symptoms, rather than cognitive decline, that increase the burden on caregivers [3]. Apathy is the most common neuropsychiatric symptom in AD and is reportedly present in 72% of patients with the disease [4]. Apathy causes progression of cognitive deficits [5] and a decline in quality of life [6].

Levy and Czernecki [6] defined apathy as "the quantitative reduction of self-generated voluntary and purposeful behaviours." The neurological basis of apathy is assumed to be the dysfunction of dopamine neurons in the prefrontal cortex (PFC) and basal ganglia [7]. The relationship between dopaminergic activity in the basal ganglia and apathy in patients with AD should be investigated to determine if this hypothesis is applicable to the apathy that occurs in these patients.

^{123}I-FP-CIT (*N*-δ-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl]tropane) binds to dopamine transporters in the nerve terminals of dopamine neurons. ^{123}I-FP-CIT single-photon emission computed tomography (SPECT) shows the density of presynaptic dopamine neurons projecting to the striatum, which reflects the dopaminergic activity in the striatum. Using ^{123}I-FP-CIT-SPECT, the severity of apathy in patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB) was shown to be inversely correlated with the striatal dopamine transporter binding potential (BP) value [8, 9]. This finding suggests that dysfunction of the dopamine nervous system is involved in the development of apathy in patients with PD and DLB. However, to the best of our knowledge, no studies have investigated the association between ^{123}I-FP-CIT-SPECT and apathy in AD.

The aim of this study was to determine whether or not the dopaminergic activity of the basal ganglia is associated with development of apathy in AD. We hypothesized that there is an association between the BP value on ^{123}I-FP-CIT-SPECT in the striatum and the degree of apathy in patients with AD.

Materials and Methods

Subjects

All patients admitted to the Department of Psychiatry at Hokkaido University Hospital between April 2015 and August 2018 with a diagnosis of major or mild neurocognitive disorder due to AD were eligible for inclusion in the study. The diagnosis was made using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnostic criteria by psychiatrists with at least 5 years of experience. Patients with other types of dementia as a comorbidity, those taking antidepressants or drugs that could affect the results of ^{123}I-FP-CIT-SPECT [10], and those with overt parkinsonism were excluded. Parkinsonism was evaluated by neurologists with at least 10 years of experience. All patients underwent a psychiatric examination, brain magnetic resonance imaging (MRI), ^{123}I-FP-CIT-SPECT, and routine blood and cognitive function tests.

Assessments of Apathy and Cognition

The Apathy Evaluation Scale Informant-Japanese version (AES-I-J) was used to evaluate apathy. The reliability and validity of this tool have been confirmed previously [11]. The AES-I-J consists of 18 questions, each of which is answered on a 4-point scale, giving a possible score of 18–72 points. The higher the score, the more severe the apathy. General cognitive function was assessed by means of the Mini-Mental State Examination (MMSE). Specific cognitive functions were assessed using the Neurobehavioral Cognitive Status Examination.

Image Acquisition and Analysis

SPECT images were acquired 3 h after injection of 167 MBq of ^{123}I-FP-CIT. The SPECT system used was a 3-head gamma camera (GCA 9300R, Canon Medical Systems, Tochigi, Japan) with an ultra-high-resolution fan-beam collimator. SPECT data acquisition involved a 90 × 120 s view over 360° continuous acquisition, a matrix size of 128 × 128, a pixel size of 1.72 mm, and an imaging time of 28 min (8 rotations). Filtering was performed using a Butterworth filter (order, 8; cut-off, 0.13 cycles/pixel). The images were reconstructed using ordered subset expectation maximization with 4 iterations and 15 subsets. The MRI scans were obtained using a 3-Tesla scanner (Achieva 3.0T TX, Phillips, Amsterdam, The Netherlands) within 1 week of SPECT imaging.

To quantitatively evaluate the ^{123}I-FP-CIT-SPECT images, fluid-attenuated inversion recovery-weighted MRI and ^{123}I-FP-CIT-SPECT images were coregistered using a Fusion Viewer (AZE Ltd., Tokyo, Japan). Each magnetic resonance (MR) image was normalized to the Montreal Neurological Institute standard brain using Statistical Parametric Mapping (SPM)12 (MathWorks, Natick, MA, USA) running on MATLAB 2018a for Mac (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, London, UK). The equation used to normalize the MRI data was applied to the ^{123}I-FP-CIT-SPECT images. Regions of interest (ROIs) in both the caudate nuclei and putamen were set using the atlas (labels_Neuromorphometrics.nii) in SPM12. ROIs were also created in the occipital lobe bilaterally by combining the superior occipital gyrus, middle occipital gyrus, inferior occipital gyrus, occipital pole, and occipital fusiform gyrus regions in the same atlas, and set as a reference area.

MR, ^{123}I-FP-CIT-SPECT, and ROI images for each subject were overlaid using MRIcro software and confirmed to be visually compatible. The SPECT value in each ROI was obtained from the normalized ^{123}I-FP-CIT-SPECT image using the MarsBaR 0.44 running on SPM12. The BP value at each position in the striatum was calculated using the following equation: (mean striatal SPECT value – mean SPECT value in the occipital lobe)/(mean SPECT value in the occipital lobe).

Statistical Analysis

The relationship between BP values and AES-I-J scores was investigated using Spearman's rank correlation coefficient. Previous studies have shown that age and symptoms of depression affect the dopamine transporter level in the striatum [9, 12]. We also examined the ability of the MMSE to exclude the general effect of progression of AD. A partial correlation test was performed for age, MMSE score, or the Geriatric Depression Scale (GDS) score to determine if these factors affect the correlation between the BP value and the AES-I-J points. A p value <0.05 was considered statistically significant. Marginal statistical significance was accepted at $0.05 \leq p < 0.1$. All statistical analyses were performed using *R* for Mac v3.5.3 (*R* Development Core Team, Vienna, Austria).

Results

Twenty-eight patients had a diagnosis of major or minor cognitive impairment due to AD during the study period. Five patients were excluded due to a lack of imaging or AES-I-J data, and 4 were excluded because they were taking antidepressants at the time the dopamine transporter images were acquired. This meant there were data available on 19 patients for inclusion in the analysis. Eighteen of these patients had major cognitive impairment and 1 had minor cognitive impairment. Demographics and clinical data are shown in Table 1.

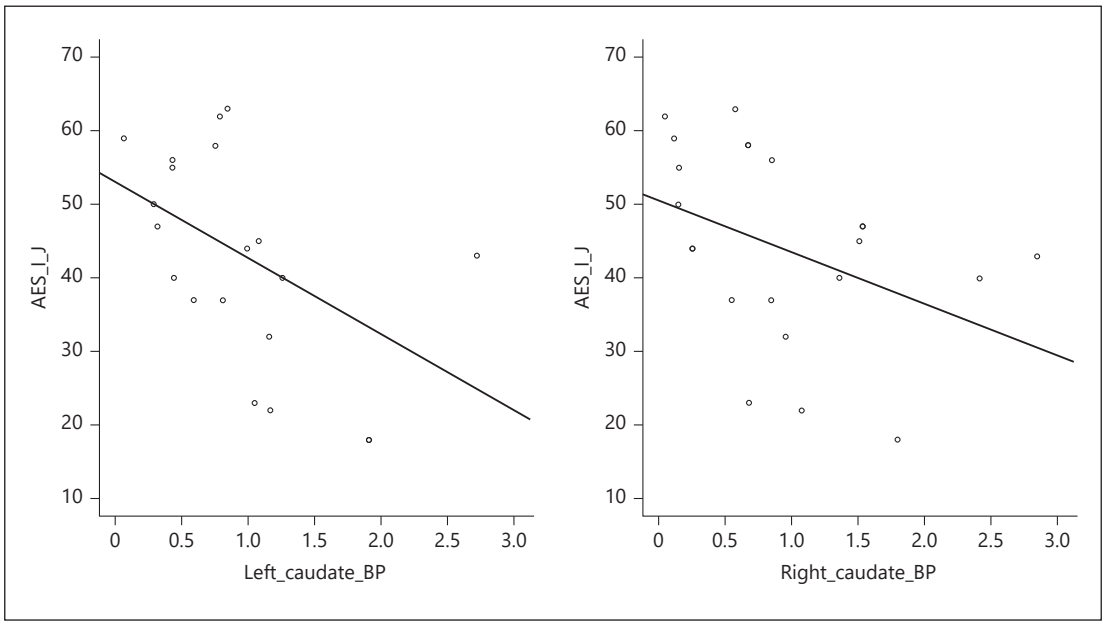

Fig. 1. Scatter plots with approximate straight lines for the AES-I-J score and BP value in the left caudate nucleus (**a**) and right caudate nucleus (**b**).

Table 1. Demographics and clinical characteristics of 19 patients

Age, years	76.9 (8.8)
Females/males, *n*	11/8
Disease duration, years	2.8 (2.3)
MMSE score	20.3 (4.7)
GDS score	3.5 (3.1)
AES-I-J score	43.7 (13.5)
BP value	
Right caudate nucleus	0.97 (0.78)
Left caudate nucleus	0.90 (0.62)
Right putamen	1.90 (0.70)
Left putamen	1.99 (0.70)

Values are expressed as mean (SD), unless indicated otherwise. AES-I-J, Apathy Evaluation Scale Informant-Japanese version; BP, binding potential; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

Figure 1 shows a scatter plot with an approximate straight line for the AES-I-J score and BP value in each striatal region. Spearman's rank correlation coefficient analysis revealed a moderate but statistically significant inverse correlation between the AES-I-J score and the BP value in both caudate nuclei (right caudate nucleus: $r = -0.532$, $p = 0.019$; left caudate nucleus: $r = -0.581$, $p = 0.009$; Table 2). No correlation was observed in the putamen. Partial correlation tests for age and MMSE and GDS scores confirmed that the inverse correlation between the BP value and the AES-I-J score remained significant in the left caudate nucleus ($r = -0.530$, $p = 0.035$). A marginally significant inverse correlation was observed in the right caudate nucleus ($r = -0.445$, $p = 0.084$).

Table 2. Correlation between AES-I-J scores and BP values in the striatum

	Correlation coefficient (r)	p value of correlation
Right caudate nucleus	–0.532	**0.019**
Left caudate nucleus	–0.581	**0.009**
Right putamen	–0.227	0.351
Left putamen	–0.232	0.340

Significant differences are indicated in bold type. AES-I-J, Apathy Evaluation Scale Informant-Japanese version; BP, binding potential.

Discussion

This study demonstrated a moderate inverse correlation between the AES-I-J score and striatal BP value on ^{123}I-FP-CIT-SPECT images in patients with AD. This result remained after partial correlation tests for age and MMSE and GDS scores. This is the first study to demonstrate an association between apathy and striatal dopaminergic function on ^{123}I-FP-CIT-SPECT images in patients with AD.

Levy and Dubois [7] hypothesized that the mechanisms causing apathy may lie in circuits within the PFC-basal ganglia circuit. Previous studies on patients with PD have shown an association between apathy and the functioning of the PFC using FDG-PET[13], and an association between apathy and dopaminergic dysfunction in the caudate nucleus using ^{123}I-FP-CIT-SPECT [8]. There has been a report of a correlation between apathy and hypoperfusion of the PFC in AD detected on ^{99m}Tc-ECD SPECT [13]. However, no studies have demonstrated a relationship between apathy and dopaminergic dysfunction in the basal ganglia. David et al. [14] reported an association between dopaminergic dysfunction in the left caudate nucleus and apathy in a ^{123}I-FP-CIT-SPECT study which included 14 patients with AD and 8 with DLB. However, our study involved exclusively patients with AD and still showed a correlation between apathy and dopaminergic dysfunction in the caudate nucleus. These findings suggest that the PFC-basal ganglia circuit is involved in the pathogenesis of apathy in AD, as is the case in PD and DLB.

Previous studies have demonstrated the deposition of amyloid β or tau pathology in the striatum in patients with advanced AD [15, 16]. Attems et al. [17] demonstrated that patients with AD had a high rate of α-synuclein pathology, which caused loss of dopamine neurons in the nigrostriatal pathway. Their results and our study findings suggest that variable amounts of striatal dopamine neurons might be lost in AD, which leads to apathy of varying degrees of severity.

Our study demonstrated a significant inverse correlation between ^{123}I-FP-CIT-SPECT in the left caudate nucleus and apathy, and a marginally significant inverse correlation in the right caudate nucleus. Previous studies of the relationship between apathy and the activity of the caudate nucleus have found discordance between the left and right sides. Two studies that used ^{123}I-FP-CIT-SPECT showed an association between dopaminergic dysfunction in the right caudate nucleus and apathy in patients with PD or DLB [8, 9]. In contrast, David et al. [14] demonstrated a correlation between ^{123}I-FP-CIT-SPECT BP values in the left caudate nucleus and the clinical dimension of lack of interest by means of an Apathy Inventory in their patients with AD and DLB.

From the perspective of laterality of disease progression, PD develops as motor symptoms unilaterally [18] whereas AD progresses to brain atrophy bilaterally [19]. Previous studies using ^{123}I-FP-CIT-SPECT have suggested an association between unilateral motor symptoms

and asymmetry of reuptake in the caudate nuclei in PD [8, 20]. In contrast, functional and structural imaging studies on patients with DLB reported both bilateral and unilateral results [21, 22]. Patients with AD were also found to have a unilateral decrease in volume or blood flow in the caudate nucleus [22, 23]. Overall, although laterality of disease progression in previous studies may provide clues regarding the laterality of dopaminergic activity in the caudate nucleus, not all the findings to date can be explained from this perspective and further research is warranted.

This study has some limitations. First, the sample size was small and there was no control group. A study of a larger sample that includes a control group matched for age and sex is warranted. The second limitation is that 4 of our subjects were taking cholinesterase inhibitors. Although these agents do not directly affect the results of ^{123}I-FP-CIT-SPECT [24], it is possible that they ameliorate apathy by augmenting cholinergic function in the frontal areas of the brain [25]. The AES-I-J scores may thus have been abnormally low in these 4 patients. However, the results were similar (right caudate nucleus: $r = -0.565$, $p = 0.056$; left caudate nucleus: $r = -0.757$, $p = 0.004$) when we analyzed our study data after excluding the patients taking cholinesterase inhibitors.

Conclusion

We showed a relationship between dopaminergic impairment in the striatum and apathy in AD, as has already been identified in PD and DLB. Our results suggest that dysfunction in the dopamine system within the PFC-basal ganglia circuit might be the cross-diagnostic pathological basis of apathy. From this point of view, it might be possible to develop a common treatment strategy for apathy in patients with these diseases. Further studies, including more subjects with AD, healthy controls, and patients with DLB and PD are required to complement the results of this study.

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Statement of Ethics

The study protocol was approved by the Hokkaido University Institutional Review Board. Written informed consent was obtained from the patient or family before enrolment in the study.

Conflict of Interest Statement

The authors report no financial or other relationship that is relevant to the subject of this article. N.U. received honoraria from Japan Medi-Physics and Tanabe Mitsubishi Pharma. N.H. received honoraria from Janssen Pharmaceutica, Yoshitomi Yakuhin, Otsuka Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma, Novartis Pharma, and Meiji Seika Pharma. T.I. received honoraria from Dainippon Sumitomo Pharma and Otsuka Pharmaceutical. H.N. received honoraria from Astellas, Dainippon Sumitomo Pharma, Meiji Seika Pharma, and Otsuka Phar-

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Author Contributions

N.U., T.M., Y.O., and H.N. acquired the scans and other data. N.U., N.H., T.T., and T.S. analyzed the data. N.U. wrote the article and N.H., S.N., and I.K. edited the manuscript. All authors reviewed the article and approved its submission.

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