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# Decreased striatal $D_2$ receptor density associated with severe behavioral abnormality in Alzheimer's disease

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***Objectives:*** Since patients manifesting behavioral and psychological symptoms of dementia (BPSD) are a burden for their families and caregivers, the underlying neurobiological mechanism of this condition should be clarified. Using positron emission tomography (PET), we previously reported that wandering behavior in dementia was associated with a disturbed dopaminergic neuron system. We herein investigated the relationship between the severity of BPSD and the striatal $D_2$ receptor density in Alzheimer's disease (AD). ***Methods:*** Ten patients with probable AD as per the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the AD and Related Disorders Association (ADRDA) criteria and five normal subjects were examined with PET. The tracer used was [$^{11}$C]raclopride ($D_2$ antagonist). The uptake of [$^{11}$C]raclopride was calculated as the estimation of binding potential (BP) of the striatum to the cerebellum. The AD patients were institutionalized in multiple nursing homes, and their BPSD were evaluated by the Behavioral Pathology in AD Frequency Weighted Severity Scale (BEHAVE-AD-FW) scale (Reisberg). ***Results:*** There was a significant inverse Spearman's correlation between BEHAVE-AD-FW score and the BP, especially between the score of the behavioral domain and the BP values. The BP was found to be lower in severer BPSD patients. ***Conclusions:*** Patients with AD who manifest severe BPSD may have some dysfunction of striatal dopamine metabolism compared with those without BPSD.

**Key words:** Alzheimer's disease, dopamine, BPSD

## INTRODUCTION

REFLECTING the aging of the world's population, the number of elderly persons with AD and other dementias is increasing. Dementia is associated with cognitive disability and behavioral and psychological symptoms of dementia (BPSD). According to the consensus statement from the International Psychogeriatric Association,[1] behavioral symptoms are usually identified on the basis of observation of patients, and include physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviors, sexual disinhibition, hoarding, cursing and shadowing. Psychological symptoms are usually mainly assessed based on interviews with patients and relatives. These symptoms include anxiety, depressive mood, hallucinations and delusions. BPSD is considered to be a syndrome of the symptomatic domain which has some relation to psychological and neurochemical changes, unlike the cognitive and functional domain which is temporally linear with progressive brain change.[2]

Two distinct domains of symptomatology can be

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**Table 1** Demographics of the study population

| ID | Diagnosis | BEHAVE-AD-FW | Age (y) | Sex | MMSE | WAIS-R | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | IQ | VIQ | PIQ |
| 1 | AD | 18 | 68 | F | 4 | ND | ND | ND |
| 2 | AD | 15 | 78 | F | 8 | 71 | 73 | 73 |
| 3 | AD | 23 | 80 | F | 5 | <60 | <60 | <60 |
| 4 | AD | 21 | 81 | F | 26 | 98 | 100 | 95 |
| 5 | AD | 3 | 87 | F | 19 | 95 | 96 | 94 |
| 6 | AD | 35 | 96 | F | 10 | <60 | <60 | <60 |
| 7 | AD | 23 | 80 | F | 14 | <60 | <60 | <60 |
| 8 | AD | 31 | 76 | M | 15 | <60 | <60 | <60 |
| 9 | AD | 9 | 78 | F | 17 | 86 | 79 | 95 |
| 10 | AD | 16 | 79 | F | 20 | 95 | 93 | 98 |
| 11 | Normal | none | 82 | F | 27 | 98 | 102 | 94 |
| 12 | Normal | none | 74 | F | 30 | 106 | 98 | 113 |
| 13 | Normal | none | 69 | F | 30 | 121 | 124 | 114 |
| 14 | Normal | none | 70 | M | 25 | 123 | 116 | 126 |
| 15 | Normal | none | 90 | F | 30 | 69 | 67 | 75 |

AD = Alzheimer's disease, BEHAVE-AD-FW = behavioral pathology in AD frequency weighted severity scale, M = male, F = female, MMSE = mini-mental-state examination, WAIS-R = Wechsler adult intelligent scale-revised, IQ = inteligence quotient, VIQ = verbal IQ, PIQ = performance IQ, ND = no data

identified over the course of the AD, a cognitive domain and a noncognitive behavioral domain, which are based on different neurobiological mechanisms. Because there are several differences in the nature, pathophysiology, course and postulated treatments for the two symptomatic domains, these two should not be mixed in the assessments. The nature of behavioral disturbance in AD is different from that seen in other illness entities such as schizophrenia and depression. Thus the assessment scale should include specific, important and frequent noncognitive behavioral symptoms manifested in AD, such as sleep disturbance, anger, verbal outbursts, physical violence, repetitive queries by patient, other anxieties and phobias.[3]

There are two scales for assessing the grade of the BPSD, i.e., the Behavioral Pathology in Alzheimer's disease (BEHAVE-AD)[4] and the Neuropsychiatric Inventory (NPI).[5] The Behavioral Pathology in AD Frequency Weighted Severity Scale (BEHAVE-AD-FW)[6] is specifically designed to assess BPSD symptoms that are of relevance for AD and related dementing disorders, whereas the NPI includes symptoms and symptomatic categories that are not of relevance for AD patients such as elation/euphoria, and complaints of shortness of breath.[6] Since the nature of behavioral disturbance in AD is different from that seen in other illness entities,[3] we used the scale BEHAVE-AD-FW in this study. Standardization of the Japanese version has been performed.[7]

Since patients manifesting symptoms of BPSD are a burden for their families and caregivers,[8,9] and since the quality of life of such patients is worsened by earlier[4] and/or increasing[6] institutionalization, the underlying neurobiological mechanism of this condition should be clarified. Pizzolato et al.[10] showed that striatal dopamine $D_2$ receptor was reduced in AD using [$^{123}$I]IBZM. Using positron emission tomography (PET), we previously reported that wandering behavior was associated with decreased fronttemporal glucose utilization and striatal dopamine metabolism (decreased DA uptake and increased $D_2$ receptor density).[11] Hirono et al.[12] showed that the depression score of the NPI was correlated with glucose metabolism in the bilateral superior frontal and left anterior cingulate cortices. Mega et al.[13] found hypoperfusion in the dorsolateral frontal cortex and left anterior cingulate in the psychotic group.

According to these previous studies, the relationship between the striatum and the neocortex seems to be important. We hypothesized that the behavioral symptoms in AD would be the result of ongoing changes in the balance of the neurotransmitter system, especially the dopaminergic system, in addition to well-known decrements in cholinergic functioning in AD.[14] The aim of the present study was to evaluate the relationship between BPSD and the neurobiological status of striatal dopamine receptors in patients with AD.

## METHODS

*Subjects*

Ten patients with probable AD as per the NINCDS-ADRDA[15] criteria with mild to moderate severity of dementia, and five normal subjects were studied. Their ADL activities, such as walking ability and self hygiene, were well preserved and their Barthel Index[16] was over 65 points. Table 1 shows the demographics of the subjects. All the patients received MRI scans and none of them had

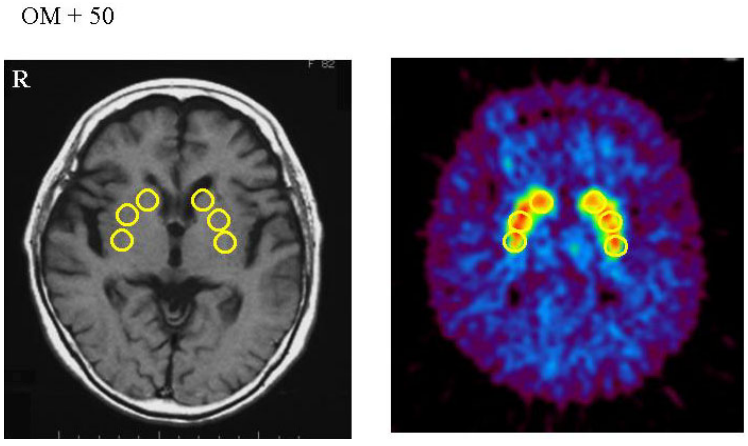


**Fig. 1** ROI-figure and application for case 11. Left = MRI image of case 11. Right = PET image of case 11. OM = orbito-meatal line, Yellow circles = ROI applied for striatal part.

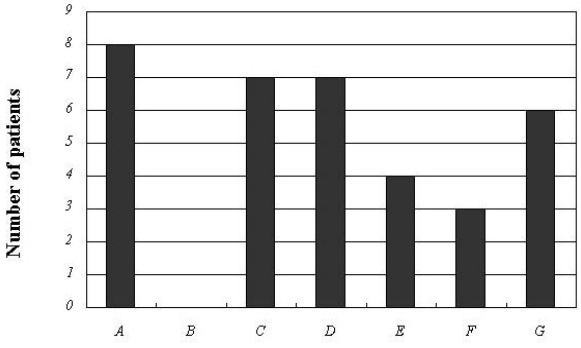


**Fig. 2** Frequencies of BEHAVE-AD-FW subcategory observed in patients. A; Paranoid and delusional ideation, B; Hallucinations, C; Activity disturbances, D; Aggressiveness, E; Diurnal rhythm disturbances, F; Affective disturbance, G; Anxieties & phobias. BEHAVE-AD-FW = the Behavioral Pathology in AD Frequency Weighted Severity Scale.

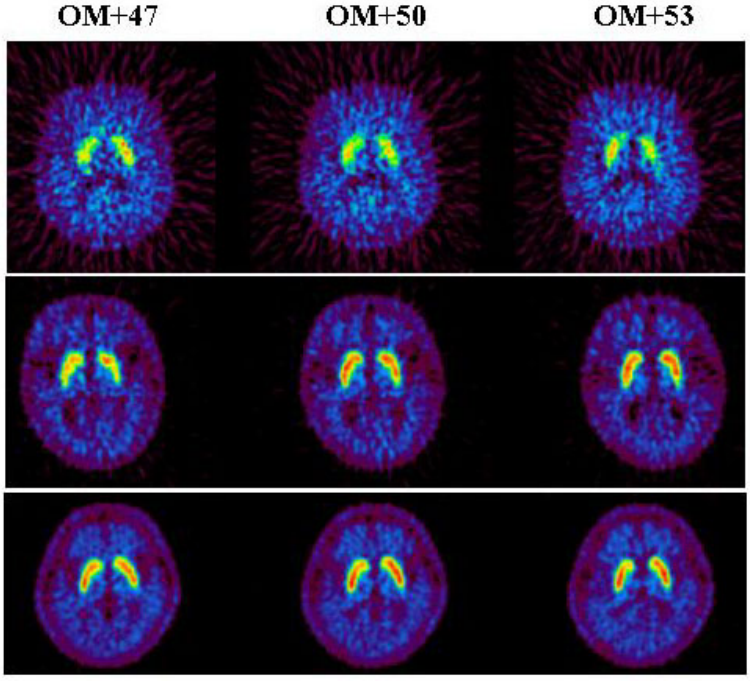


**Fig. 3** PET images of [$^{11}$C]raclopride. A patient who manifested severe BPSD (*upper row*, BPSD: 23) had lower eBP (R/L = 1.51/1.35), while one with mild BPSD (*middle row*, BPSD: 3) had relatively high eBP (R/L = 2.54/2.45). A normal subject (*bottom*) showed high eBP values (R/L = 2.93/2.71). PET = Positron Emission Tomography.

cerebrovascular diseases in the striatum.

None of the patients showed visual symptoms, or extrapyramidal signs such as rigidity, and none met the criteria for the clinical diagnosis of probable or possible dementia with Lewy bodies (DLB).[17] The Medical Ethics Committee of the Cyclotron Radioisotope Center at Tohoku University approved this study, and written informed consent was received from all the normal subjects and the families of the patients.

*Behavioral observations*

We used the BEHAVE-AD-FW,[6] consisting of 7 subcategories: A, Paranoid and delusional ideation; B, Hallucinations; C, Activity disturbances; D, Aggressiveness; E, Diurnal rhythm disturbances; F, Affective disturbance; G, Anxieties and phobias. Categories A, B, C, D, E, F, G have 7 5, 3, 3, 1, 2, 4 items, respectively. The total scores were calculated by multiplying the rating severity (0 to 3) by the frequency (1 to 4) for each, the global rating score (0 to 3) being added.

*[$^{11}$C]raclopride PET*

The binding potential (BP) of $D_2$ receptors was assessed using a SET-2400 (Shimadzu Ind., Japan) camera and [$^{11}$C]raclopride[18] as a radioligand. Scans were performed following a bolus infusion of 148–407 MBq (3.7–5.6 MBq/kg) of [$^{11}$C]raclopride, the mean specific activity of which was 122 GBq/$\mu$mol (range 47–386). PET data were acquired up to 90 minutes after injection in the 3D mode with the septa retracted, and data were corrected for decay and tissue attenuation using a $^{68}$Ge/$^{68}$Ga rotating rod source of 370 MBq. Image reconstruction was carried out using 3D back projection onto 128 × 128 × 63 pixel images with practical resolutions of 6.3, 6.3, 8.0 mm at full width half maximum in tangentional, radial, and axial directions respectively. Scatter fractions were numerically corrected using a model based on estimation of scatter events. Regions of interest (ROIs) were drawn on three adjacent slices for both the left and right striatum (caudate and putamen) of 3 round figures along the shape of the striatum in 24 pixels each, and for the cerebellum of 61 pixels each, which were clearly identifiable (Fig. 1).

The ROIs were applied to the summation images acquired from 40 to 60 minutes. The positions of the ROIs were determined by two neuroradiologists with reference to the corresponding MRI images, blind to both to the diagnosis and the BPSD status. The estimation of BPs (eBP) were calculated assuming that tracer kinetics were at transient equilibrium with cerebellum counts as a reference. Since the two eBP values assessed by the two neuroradiologists were not statistically different, standard deviations ranging from 2 to 14% (average 5.0%), we used the average values for analysis.

The ratio of counts in the (striatum minus cerebellum)/cerebellum during the period of pseudoequilibrium was used as an estimate of the $B_{max}/K_d$ of [$^{11}$C]raclopride for dopamine $D_2$ receptors[19–23] in this paper. This is based on the assumption that the cerebellum is devoid of specific binding (C), whereas the striatal (S) counts reflect specific binding of the ligand to $D_2$ receptors in addition to the non-specific and free ligand binding. The amounts of free and non-specifically bound tracers are assumed not to differ between these two regions. Based on these assumptions, it can be shown that the [S − C]/C ratio closely reflects BP, that is the ratio of $B_{max}/K_d$, where $B_{max}$ is the total concentration of $D_2$ receptors, and $K_d$ is the dissociation constant for the ligand.[24,25]

## RESULTS

Figure 2 illustrates the features of the BPSD observed in the AD patients. Paranoid and delusional ideation (A), Activity disturbance (C) and Aggressions (D) were shown by most patients. No patients showed hallucination in this

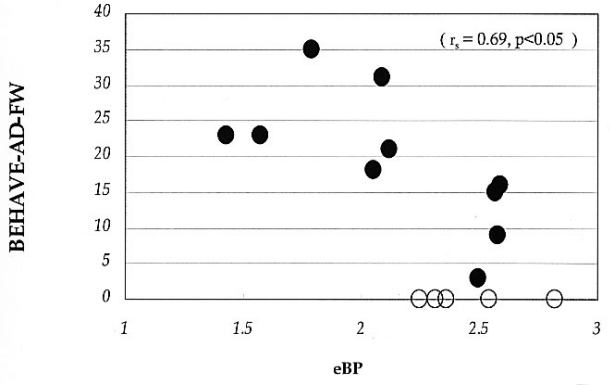


**Fig. 4** Relationship between BEHAVE-AD-FW score and eBP. Closed circles indicate AD patients; open circles indicate normal subjects. There was a significant inverse Spearman's correlation between the BEHAVE-AD-FW score and the eBP. $r_s$ = Spearman rank correlation coefficient, BEHAVE-AD-FW = the Behavioral Pathology in AD Frequency Weighted Severity Scale.

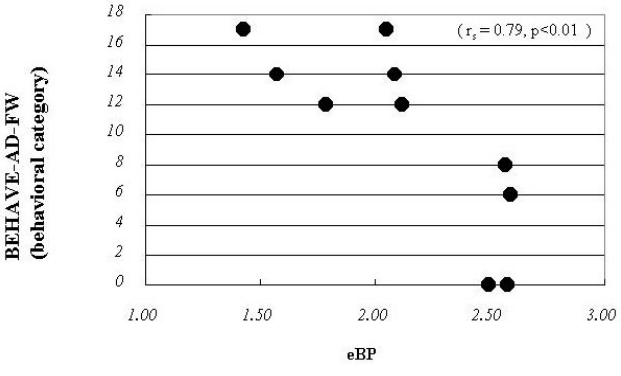


**Fig. 5** Relationship between subcategory score and eBP. There was a significant inverse Spearman's correlation between the BEHAVE-AD-FW subcategory summation score (C, D, E) and eBP in AD patients.

study. There was no correlation between the eBP values and MMSE scores of AD patients.

Figure 3 illustrates the PET images of typical cases. Patients who manifested severe BPSD had lower eBP, and those with mild BPSD had relatively high eBP. Normal subject showed high eBP values.

Figure 4 illustrates the correlation between the BEHAVE-AD-FW scores and the eBP. We plotted the average eBP values of both sides. There was a significant inverse Spearman's correlation ($p < 0.05$) between the BEHAVE-AD-FW scores and average eBP values. For each subcategory, categories C (activity disturbance) and E (diurnal rhythm disturbances) showed a significant inverse correlation ($r_s = 0.57, 0.59$ respectively, $p < 0.05$, one-tail) with the eBP values.

We plotted the eBP values of both sides separately: there was also a significant inverse Spearman's correlation ($r_s = 0.69$, $p < 0.05$). No laterality was found in this analysis.

Since the BEHAVE-AD-FW includes the two domains (psychological and behavioral), we analyzed those two domains separately: there was a significant inverse correlation between the behavioral domain (the summation of categories C, D and E) scores and the values of eBP ($p < 0.01$, Fig. 5). However, no correlation was found for the psychological domain (the summation of the categories A, B, F and G).

## DISCUSSION

In this study, we found that AD patients manifesting severe behavioral abnormality (behavioral domain of the BEHAVE-AD-FW) showed decreased dopamine $D_2$ receptor density. No delusional symptoms were observed in the patients (Fig. 2), which is compatible with previous findings. In general, hallucinations are less frequently observed than paranoid and delusional symptoms in AD,[26,27] but recurrently observed in a subtype of dementia with Lewy bodies.[17]

*Methodological issues*

[$^{11}$C]raclopride is widely used for *in vivo* measurement in research on dopamine $D_2$-like receptors in both pharmacological and neurobiological studies. This ligand has high affinity and selectivity for $D_2$-like receptors, but the affinity is less than that of [$^{11}$C]nemonapride.[28,29] This may be the cause of the results which differ from those of other studies using [$^{11}$C]nemonapride or [$^{11}$C]methylspiperone. By applying the ROIs, the dorsal and ventral components of the striatum could be assessed concurrently. As described earlier, we used the BEHAVE-AD-FW, not the NPI, because the BEHAVE-AD-FW includes only symptoms and symptomatic categories that are of relevance for AD, whereas the NPI includes symptoms and symptomatic categories that are not of such relevance.[6]

*AD and dopaminergic system*

Regarding human $D_2$ receptors, using [$^{123}$I]IBZM, Pizzolato et al.[10] found that striatal dopamine receptors were reduced in AD. In a recent PET study on the dopaminergic system, the striatal reuptake of dopamine was found to be reduced with reference to extrapyramidal symptoms,[30] but no patients showed obvious extrapyramidal symptoms in the present study. In AD patients, there may be some deterioration of both pre-synaptic and post-synaptic striatal dopaminergic activities. We previously reported that wandering behavior was correlated with an increase in striatal dopamine $D_2$ receptor using [$^{11}$C]nemonapride.[11] However, another study showed no reduction in the uptake of [$^{11}$C]raclopride in the caudate nucleus of early AD and found that striatal $D_1$ and $D_2$ receptors are differentially affected.[31]

Ishiwata et al.[29] reported that the uptake of [$^{11}$C]raclopride in the quinolinic acid-lesioned rat striatum was decreased, but that of [$^{11}$C]nemonapride, which also has affinity to other subtypes of dopamine receptors, was increased. Ishiwata et al's results may explain the discrepancy between our previous report and the other report. Namely, the tracer [$^{11}$C]raclopride is more specific to the striatum than [$^{11}$C]nemonapride.

Another reason is probably the method of assessment; the previously reported BPSD was mainly wandering behavior, whereas the patients in this study were evaluated by the BEHAVE-AD-FW systematically. So the relationship between the BP and BPSD may be different from that of the BP and wandering behavior alone.

*Behavioral abnormality and dopamine system*

There was a significant inverse Spearman's correlation between the eBP values and the BEHAVE-AD-FW summation scores of the behavioral domain, not the psychiatric domain. Thus, the changes of the striatal dopaminergic system may be responsible for the BPSD symptoms observed in the behavioral domain, and not for those observed in the psychiatric domain. Another possibility is that there may be another change in the brain responsible for the BPSD symptoms observed in the psychiatric domain which cannot be assessed by PET using [$^{11}$C]raclopride. There has been no previous report on the relationship between behavioral symptoms of dementia and striatal $D_2$-like receptor change.

Based on empirical observations and the use of neuroleptics, the dopaminergic neuron system with reference to rewarded behavior and depression has been studied. In rat studies,[32] the dopamine system has been found to be probably involved in the reward system and the motor system. A study using a chronic stress animal model of depression[33] indicated that the dopamine receptor antagonist has a reverse anti-depressant effect. As described earlier, Hirono[12] showed the relationship between the depression score and lower glucose metabolism in the bilateral frontal and left anterior cingulated cortices,

and Mega[13] showed hypoperfusion of the frontal cortex and the cingulate in the psychotic group. We previously reported[34] that the front-striatal circuit could be related to the neural network between the supra-chiasmatic nucleus. Thus there may probably be some influences on the striatal system by affected cortices in AD via the neural network.

It is far from clear that a single abnormality will suffice to explain both psychological and behavioral decrements in the patients with BPSD. There is also the problem of whether the reduction in $D_2$ receptor is the primary cause or an implicit reflection of BPSD. Further concurrent *in vivo* research is necessary to assess metabolic changes of both the dopaminergic system and cortical glucose consumption using [$^{18}$F]FDG.

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